PUSHING AGAINST THE PULL: THE IMPACT OF EMOTIONS AND APPETITIVE CUES ON SELF-CONTROL AND THE UNDERLYING NEURAL CIRCUITRY

A Dissertation

Presented to the Faculty of the Weill Cornell Graduate School

of Medical Sciences

in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

Michael Frederic Weill Dreyfuss

January 2017

PUSHING AGAINST THE PULL: THE IMPACT OF EMOTIONS AND APPETITIVE CUES ON SELF-CONTROL AND THE UNDERLYING NEURAL CIRCUITRY

Michael Dreyfuss, PhD

Cornell University 2017

The ability to withhold responses from appetitive and emotionally salient cues in the environment allows us to make decisions that favor positive long-term outcomes over immediate rewards. This capacity for self-control is an adaptive cognitive ability that requires regulation of motivational drives to action. An inability to exert self-control appropriately can relate to real-world consequences, such as poor health outcomes and undesired weight gain due to unregulated eating. Individuals vary in their ability to exhibit self-control, particularly under negative emotional influences. At the pathological extreme, total lapses in self-control can underlie behaviors such as binge eating in bulimia nervosa, which may develop during adolescence as maladaptive coping mechanisms for negative emotions. This thesis investigates how self-control and the neural circuitry underlying it develop under emotional influences over the course of adolescence and into early adulthood. Chapter one provides a framework of the neural circuitry, development and psychopathology of self-control. Chapter two examines adolescent impulsivity toward emotionally salient cues of and related changes in regional brain function during that period. Adolescence is a peak time for the emergence of psychopathologies and maladaptive behaviors (Lee et al., 2014). Chapter three asses the development of self-control and neural circuitry in bulimia nervosa under changing emotional influences from late adolescence into early adulthood. A heightened sensitivity toward food cues may relate to binge

eating in bulimia nervosa and problem eating in non-eating disordered individuals. Chapter four measures the influence of appetitive food cues under emotional influences on self-control in bulimia nervosa and across non-eating disordered individuals based on tendencies to eat when anxious. Together, these studies examine how emotional, appetitive, diagnostic and individual influences interact to influence self-control and the brain circuitry that underlies it. Chapter five synthesizes these findings and discusses implications for treatment, limitations and future directions of this work.

BIOGRAPHICAL SKETCH

Michael Dreyfuss was born in Chicago in 1986. He was raised in Evanston, IL and Wynnewood, PA until attending Columbia College of Columbia University in the City of New York. At Columbia, Michael pursued a B.A. in biochemistry with a concentration in linguistics. As an undergraduate, Michael worked in the lab of Dr. Martin Chalfie, studying mechanosensation in *C. elegans*, and founded the Columbia Linguistics Society. After his time at Columbia, he studied for a Master 1 in linguistics at l'université de Toulouse II–Le Mirail as a Fulbright Scholar. There, he studied the Occitan language and the efforts of local schools to pass the language on to future generations through bilingual primary education. While he enjoyed studying languages as a lens to understand cultures, his interested lay in the biological basis of human behavior. He returned to laboratory science to the lab of Dr. Murray Grossman at UPenn where he worked on fMRI studies of neurodegenerative aphasias. His exposure to scientific research and patient care further inspired him to pursue a career in medicine and science. He joined the Tri-Institutional MD-PhD Medical Scientist Training Program in 2011. Two years later, he had the opportunity to join Dr. BJ Casey's group in the Sackler Institute where he had the chance to use fMRI and behavioral tools to examine development of self-control. Through a collaboration with Dr. Allegra Broft's group at the Eating Disorders Clinic at Columbia University, he also used these methods to study self-control in bulimia nervosa.

ACKNOWLEDGEMENTS

BJ Casey – You have provided me with an invaluable opportunity to spend my doctoral years studying a subject I love in an enriching environment. You provided me with the resources and mentorship to grow as a scientist, and have never expected less than the best from me. For this this training and this experience, I cannot than you enough.

Allegra Broft – Thank you for your collaboration and your clinical expertise. It has been a pleasure working with you.

Conor Liston, Charles Glatt and Bruce McEwen – Thank you for your guidance and your critical evaluations throughout my doctoral training.

Tri-I MD-PhD Program – Your administrative and personal support have been a constant grounding force at this institution for me. I am fortunate to have been part of this program.

Tri-I Classmates – You are a group of intelligent, interesting and inspiring young medical researchers. It has been a pleasure and an honor being your classmate.

Aaron Heller, Niko Steinbeiss, Rebecca Jones, Cate Hartley – Thank you for your scientific and emotional support.

Ali Cohen – For being my constant lab companion.

Danielle Dellarco, May Conly, Alisa Powers, Theresa Teslovich, Anfei Li, Andre Drysdale, Hugo Decker, Dave Jonson, Dylan Gee, Melanie Silverman,

Estée Rubien-Thomas, Camille Gregory, Gloria Pedersen, Dienke Bos, Frederico Lourenço, Matthew Malter Cohen – it has been a wonderful experience to work with you.

Jon Dyke – Thank you for always finding the time to happily help me with my imaging questions and projects.

Financial Support: T32 GM007739

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 2

Chapter 1: Developmental and Individual Differences in Self Control – an Introduction

Introduction

Self-control refers to our ability to suppress inappropriate actions, emotions and desires in favor of goal-oriented ones. Putting down a piece of delicious cake because you are on a diet, illustrates how we can stop an appealing action in favor of a future goal. Resisting temptations is not easy, and circumstances may shift the balance from exhibiting successful self-control toward giving into appetitive cues like a piece of cake. Emotionally charged situations, and negative emotions may diminish our capacity for self-control. We may become particularly sensitized to appetitive cues because they pull our attention or actions away from the negative experience toward something more positive. Managing negative emotions may also reduce or deplete cognitive resources ~~a~~ thereby diminishing our capacity to control our behavior. Thus, engaging in rewarding actions like eating food may serve as a means of providing relief from these feelings when other coping mechanisms are not sufficient or available to us. We each vary in these abilities both across development and across individuals. This thesis examines how cues of potential reward (food) and threat and emotional state, both positive and negative, differentially impact self-control across development and across individuals. Neural circuitry underlying self-control is examined to constrain the interpretation of the behavioral findings.

This chapter first provides an overview of the underlying neural circuitry of self-control, followed by a brief overview of developmental and individual differences in this capacity, specifically under emotional influences. I focus

largely on the developmental periods of adolescence and adulthood when this capacity typically matures and when a number of mental illnesses that show diminished self-control peak in prevalence (Ronald C. Kessler et al., 2005). I then examine this capacity in the case of binge eating in bulimia nervosa (BN) as an extreme variant of diminished self-control during late adolescence and young adulthood.

Neural circuitry underlying self-control

Distinct but interacting neural systems are thought to mediate motivational drive and behavioral regulation. The prefrontal cortex (PFC) shares projections to and from the amygdala and ventral striatum, and the amygdala has projections to the ventral striatum and PFC (Figure 1.1, Casey, 2015). The drive to take action, to identify and obtain rewards in the environment, and the capacity to withhold such responses are associated and modulated by this circuitry. The prefrontal cortex is largely associated with top-down control over behavior and emotion regulation, while the ventral striatum, which is implicated in motivated behavior and responding to reward outcomes. The amygdala has unidirectional projections to the ventral striatum (Friedman, Aggleton, & Saunders, 2002; Russchen, Bakst, Amaral, & Price, 1985). Glutamatergic pathways from the basolateral amygdala to the ventral striatum have been shown to promote motivated behavioral responding (Stuber et al., 2011).

Motivational drive is largely associated with dopamine release in subcortical structures, particularly the ventral striatum (Robbins & Everitt, 1992). This region is rich in dopamine receptors D1 and D2 and dopaminergic projections from the ventral tegmental area of the thalamus (Haber & Knutson, 2010). Dopamine release in this area from the ventral tegmental area (VTA)

occurs in response to primary rewards such as the receipt of food (Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Small, Jones-Gotman, & Dagher, 2003), psychostimulants (Breiter et al., 1997; Drevets et al., 2001; Volkow et al., 1999) and financial gains (Breiter, Itzhak, Kahneman, & Shizgal, 2001; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). The ventral striatum and the amygdala appear particularly responsive during the anticipation, rather than actual receipt of rewards (Knutson, Fong, Adams, Varner, & Hommer, 2001), while the orbitofrontal cortex (OFC) is active during both anticipation and receipt (O'Doherty, Deichmann, Critchley, & Dolan, 2002). The ventral striatum thus appears to be more involved in wanting than liking rewards (Berridge, 1996, 2009), implicating it in reward drive rather than hedonic pleasure. Dysregulation of this region is associated with disorders of unregulated consumption including drug addiction and binge eating (Di Chiara et al., 2004), which may share a common increased release of and sensitivity to dopamine (Hadad & Knackstedt, 2014). This region has been shown to relate directly to behavioral outcomes. Activity in the ventral striatum predicts likelihood of giving into cravings for food (Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014) and psychostimulants (Li & Sinha, 2008), suggesting a direct relationship between this region and degree of reward drive.

The PFC is associated with moderating activity in the ventral striatum and amygdala in a way that can inhibit motivated responding. Damage to the PFC by lesions and progressive neurodegeneration such as in frontotemporal dementia have been associated with disinhibited behavior and impaired decision making (Bechara, Tranel, & Damasio, 2000; Dias, Robbins, & Roberts, 1996; Rascovsky et al., 2011). Inhibiting activity in the lateral PFC by transcranial magnetic stimulation has been shown to result in a preference for immediate over long-

term rewards (Figner et al., 2010). Better PFC function, in contrast, is associated with improved restraint. Cocaine users and cigarette smokers show greater recruitment of PFC when successfully regulating cravings (Brody et al., 2007; Kober et al., 2010; Volkow et al., 2010). Functional magnetic resonance imaging (fMRI) of response inhibition have consistently shown recruitment of prefrontal regions, particularly inferior frontal gyrus (IFG; Menon et al., 2001; Rubia et al., 2003). Greater IFG activity during successful response inhibition on go/nogo tasks has been shown to relate to lower trait impulsivity (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003), and better response inhibition (Somerville, Hare, & Casey, 2011), leading to the suggestion that this region in particular may serve as a brake on approach behavior (Aron, Robbins, & Poldrack, 2004, 2014).

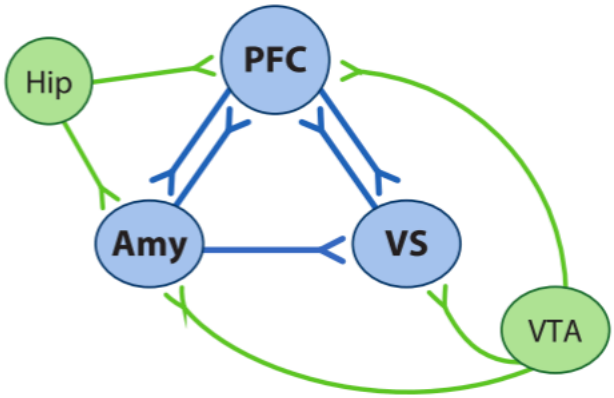

Figure 1.1 Schematic of neural circuitry underlying self-control. Prefrontal cortex (PFC) has projections to and from the amygdala (Amy) and ventral striatum (VS). The amygdala has projection to the ventral striatum (VS) but not vice-versa. Dopaminergic projections from the ventral tegmental area (VTA) and hippocampus (Hip) modulates activity of this circuitry.

Top-down interactions between the PFC and subcortical circuitry has been shown to modify responses cognitive and behavioral output. Activity in the PFC

has been shown to predict decreases in drug cravings (Kober et al., 2010), and successful regulation of food cravings (Lopez et al., 2014), which are mediated by decreasing activity in the ventral striatum. Such studies highlight the importance of understanding the connections between brain regions in successful behavioral control (Casey, 2015). Examining this frontostriatal brain circuitry therefore provides an opportunity to understand the biological basis of behavioral changes between individuals, across development and in psychopathologies characterized by recurrent problems of behavioral inhibition.

Interactions between the PFC and the amygdala are implicated in underlying successful emotion regulation, as well. Prefrontal circuitry can attenuate the response of the amygdala to negative stimuli (Buhle et al., 2014; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Ochsner & Gross, 2005), dependent on the connections between PFC and subcortical circuitry (Silvers et al., 2016; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Functional connectivity between PFC and amygdala correlates emotional regulation success (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; H. Lee, Heller, van Reekum, Nelson, & Davidson, 2012). Overlap in circuitry involved in regulating emotional responses and behavior may relate to impairments in self-control observed under negative emotional influences (Heatherton & Wagner, 2011).

Development of self-control

Adolescence is a transitional period of emotional, cognitive and physical development during which individuals must establish a distinct identity from their care-takers. Adolescents exhibit greater reward, sensation and novelty seeking than children or adults (Douglas, Varlinskaya, & Spear, 2003; Galván, 2013; Spear, 2000; Stansfield & Kirstein, 2006), and are more impulsive than adults

(Steinberg, 2010). These characteristics provide adolescence with a heightened tendency to explore new environments, situations and relationships which may serve a purpose of creating their unique identity (Irwin & Millstein, 1992).

These factors may also predispose adolescents to engage in risky behaviors. Adolescence is a peak period for substance abuse, unsafe sexual practices, and driving under the influence of alcohol (Arnett, 1992; Arnett, 1999). Heightened sensation seeking and diminished impulsivity may underlie greater proclivity for gambling and substance use than adults (Chambers & Potenza, 2003; Chambers, Taylor, & Potenza, 2003). Indeed, sensation seeking has been shown to mediate the relationship between pubertal development and drug use among adolescents (Martin et al., 2002). When these behavioral patterns are established during adolescence they are more likely to persist chronically into adulthood (Williams, Holmbeck, & Greenley, 2002). Smoking, alcohol and substance abuse typically begin during adolescence (Call et al., 2002; Chassin et al., 2004; Chassin, Presson, Rose, & Sherman, 1996; K. Chen & Kandel, 1995; Resnick et al., 1997), as do binge eating behaviors (Stice, Killen, Hayward, & Taylor, 1998), and alcohol abuse is more likely to become habitual with earlier age of onset (Grant & Dawson, 1997). The persistence of these behaviors into adulthood further highlights the importance of understanding and preventing these behaviors before they start.

The dispositional changes related to elevated risk taking during adolescence may be due to a temporary imbalance between motivational and control circuitry. Subcortical structures involved in emotion and reward processing are relatively mature during adolescence, while the development and function of prefrontal cortical network involved in self-control is more protracted (Casey, Jones, & Hare, 2008; Ernst, Pine, & Hardin, 2006; Steinberg, 2010).

Changes in brain structure during this developmental period support this view. Synaptic pruning, the process by which redundant neural connections are eliminated in favor of more efficient networks (Chechik, Meilijson, & Ruppin, 1998; Chechik, Meilijson, & Ruppin, 1999), occurs at different rates in different regions of the brain. Post-mortem autopsies examining synaptic density in human brain tissue (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997) and non-human primate brains (J. Bourgeois & Goldman-rakic, 1994; J. P. Bourgeois, Jastreboff, & Rakic, 1989) have provided evidence that pruning in prefrontal structures of the cerebral cortex continues to occur from late childhood through adolescence, after primary motor, visual and cortex have reached maturity. Structural MRI studies using measures of gray matter density and cortical thickness to measure changes in gray matter in vivo with age have yielded congruent results. Cortical thickness and gray matter density continue to decrease in prefrontal as well as parietal and temporal association cortices implicated in higher level cognitive functions after other cortical areas (Gogtay et al., 2004; Sowell, 2004). These findings would indicate that prefrontal cortex may not be fully efficient at adult levels. White matter in the brain continues to develop throughout adolescence and early adulthood (Asato, Terwilliger, Woo, & Luna, 2010; Giedd et al., 1999; Gogtay et al., 2004), as does myelination (Wozniak & Lim, 2006), suggesting immature connections between brain regions that may reflect a relative deficiency in the ability for prefrontal cortex to effectively communicate and exhibit control on subcortical structures. Furthermore, The density of dopamine receptors D1 and D2 peaks during adolescence in the ventral striatum (Seeman et al., 1987; Tarazi & Baldessarini, 2000; Teicher, Krenzel, Thompson, & Andersen, 2003) and declines in adulthood. D1 and D2 receptor density does not peak in the prefrontal cortex until early adulthood in contrast (Weickert et al., 2007), resulting in a potential imbalance in the

sensitivity to this neurotransmitter between these brain regions. Together, these structural, synaptic and neuromodulatory changes provide evidence for a brain in transition between childhood and adolescence that is maturing at different rates, resulting in temporary imbalances between the cognitive control and reward seeking neurocircuitry (Casey et al., 2008).

Paralleling structural changes, behavioral and functional neuroimaging studies have provided tools to examine how cognitive abilities mature over the course of adolescence. For many cognitive abilities, including working memory, cognitive flexibility and response inhibition, linear trajectories of improvement with age are observed from childhood into adolescence (Best & Miller, 2010; Davidson, Amso, Anderson, & Diamond, 2006). Response inhibition on antisaccade tasks appears to be mature by early adolescence (Klein & Foerster, 2001, Fukushima, Hatta, & Fukushima, 2000), with other cognitive functions reaching adult levels at later ages (Luna et al., 2004). Performance on Stroop (Adleman et al., 2002; Huizinga, Dolan, & van der Molen, 2006; Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007) and go/nogo tasks (Eigsti et al., 2006; Hooper, Luciana, Conklin, & Yarger, 2004) shows improve throughout adolescence into early adulthood when non-emotional stimuli are used. Some studies have found age-related improvements in cognitive performance to be accompanied by increased recruitment of neural circuitry on fMRI (Adleman et al., 2002; Marsh et al., 2007), implicating this activity in more effectively supporting self-control. Other studies showing behavioral improvements in inhibitory control have found that younger participants show greater and recruitment in more diffuse neural systems than adults on successful task performance (Casey, Giedd, & Thomas, 2000; Durston et al., 2002, 2006; Rubia et al., 2013), suggesting more efficient engagement of these neural systems with

increasing age (Brown et al., 2005; Wartenburger, Heekeren, Preusse, Kramer, & Meer, 2009). These different findings may be related to the experimental paradigm used (Stroop vs go/nogo), differences in analyses (correct vs incorrect trials) or may reflect a shift in which neural networks are used for successful cognitive control. Notably, increased functional connectivity between brain regions may relate to improvements in the ability to exert top-down control (Hwang, Velanova, & Luna, 2010) suggesting a more efficiently connected brain develops over adolescence.

In contrast, to these linear improvements in performance with age on simple cognitive tasks, “hot” tasks involving stimuli, outcomes or decisions that are motivationally salient show a protracted improvement with age (Prencipe et al., 2011; Tottenham, Hare, & Casey, 2011). Adolescents have difficulty ignoring emotional stimuli that are irrelevant to task performance (Grose-fifer et al., 2013), and make more uninhibited approaches to positive social cues paralleled by increased activity in the ventral striatum (Somerville et al., 2011). Changes in behavioral proclivities and neural architectures during this period may to explain their poor performance on emotionally charged tasks. A heightened sensitivity to reward appears to underlie greater approach behavior on gambling tasks (Cauffman et al., 2010; D. G. Smith, Xiao, & Bechara, 2012). Adolescents also change their behavior when rewards are involved, slowing responses on decision making tasks and recruiting increased fronto-parietal circuitry (Teslovich, Mulder, et al., 2014), suggesting that they are able to modify behavior in the face of potential gains. Decreased neural response to losses in the amygdala (Ernst et al., 2005), and hyperresponsiveness of the ventral striatum to rewards among adolescent humans (Ernst et al., 2006; Galvan, 2010; Galvan et al., 2006; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Van Leijenhorst, Moor, et al.,

2010) and rats (Laviola, Macrì, Morley-Fletcher, & Adriani, 2003) may explain a decreased response to aversive stimuli and events and heightened sensation seeking. The amygdala, which responds to negative faces and scenes on fMRI (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Pessoa, Mckenna, Gutierrez, & Ungerleider, 2002), shows increased activation to negative stimuli among teens (Hare et al., 2008; Monk et al., 2003). Approach behavior toward emotional stimuli in adolescence appears to be driven by increased activation in both of amygdala and ventral striatum, and regulated by prefrontal activity (Hare et al., 2008; Somerville et al., 2011). The sensitivity of this circuitry to rewards and emotional cues during this stage has been explained to underlie the heightened impulsive and reward sensitive behavior during this developmental stage (Hare et al., 2008; Somerville et al., 2011; Van Leijenhorst, Moor, et al., 2010). Beyond acute emotional cues, a recent study implemented a task dissociating the impact of acute and sustained emotional influences on the development of cognitive control from adolescence into adulthood (Cohen, Breiner, et al., 2016). Sustained negative emotions resulted in impaired cognitive control in adolescents relative to adults and increased recruitment of ventromedial PFC, suggesting a heightened sensitivity to threat which may interfere with behavioral control during this developmental stage. Activity in region showed decreased functional coupling with frontal and parietal regions among adolescent participants, implicating changes in a network involved in emotional and cognitive control during this time.

Dynamic changes in the connectivity between cortical and subcortical structures, and between subcortical regions is also important to examine as underlying behavioral proclivities specific to this age group (Casey, 2015). Response inhibition also involves a shift from connectivity between dorsal and

ventral striata during adolescence to connectivity between the right IFG and the dorsal striatum (Somerville et al., 2011). Activity of the amygdala is functionally coupled with the ventral striatum from early in development (Fareri et al., 2015), but exhibits dynamic changes in connectivity with cortical structure and the hippocampus over the course of development (Fareri et al., 2015; Gabard-Durnam et al., 2014), which has implications in emotion regulation (Gee et al., 2013; Perlman & Pelphrey, 2011). Structural connectivity of amygdala-cortical connections predicts amygdala response to negative emotional stimuli, which is moderated with age (Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014). Changes in cognitive and emotional brain circuitry during adolescence parallel a heightened susceptibility for poor self-control.

In summary, adolescence is a period of heightened risk taking during which behavioral and psychological patterns are established. This developmental stage is a peak period for the for the development of psychiatric disorders (Kessler et al., 2005). Adolescence and early adulthood are also a peak period and disorders that arise during this period are typically more resistant to treatment (Lee et al., 2014). Understanding what about the adolescent brain drives unnecessary risk taking and contributes to the development of these disorders is therefore particularly valuable for developing better preventions and treatments.

Individual differences in self-control

From an early age, some individuals show a willingness to withhold approaching an appetizing food reward to obtain a delayed but larger reward, while others have a tendency to prefer the immediate but smaller reward (Mischel, Shoda, & Rodriguez, 1989). These high and low delayers differ in their

capacity to suppress the desire to eat temporarily in favor of a more rewarding long-term outcome. Examining which individuals are able implement this kind of self-control is valuable in understanding real-life outcomes. Self-control predicts better emotional adjustment, more stable relationships (Tangney, Baumeister, & Boone, 2004), and better performance in school (Duckworth & Seligman, 2012). Individuals who are less impulsive are less likely to abuse alcohol and engage in risky sexual practices (Quinn & Fromme, 2010). Excessive impulsivity can also be a predisposing factor for developing psychiatric disorders, including binge eating behaviors (Claes, Vandereycken, & Vertommen, 2005; Dawe & Loxton, 2004; Kane, Loxton, Staiger, & Dawe, 2004; Kemps & Wilsdon, 2010). In a study following up on individuals who were low and high delayers as children 40 years later as adults, individuals who were low delayers as children were found to exhibit poor impulse control specifically toward positive cues as adults, suggesting that impulse control toward appetitive stimuli is relatively stable over an individual's lifetime (Casey et al., 2011). Furthermore, relative to high delayers, individuals who were low delayers as children showed heightened recruitment of IFG and ventral striatum on fMRI when successfully inhibiting responses to positive cues, implicating inefficient recruitment of control circuitry and a highly reactive motivational response as underlying poor self-control toward positive stimuli (Casey et al., 2011). These results underscore the importance of examining self-control and its underlying neurocircuitry through a lens of individual differences (Casey & Caudle, 2013).

Examining self-control over eating behavior has provided an understanding of why some individuals are more susceptible to give into food temptations than others. Appropriate drive toward food is necessary to seek out food for calories and nutrition, but unrestrained eating in the context of a high

availability of energy dense foods can lead to poor health consequence and undesired weight gain. Individual differences can predict susceptibility to overeat and related health consequences. Sensitivity to reward correlates with BMI (Franken & Muris, 2005), and is greater in obese than non-obese individuals (Nederkoorn, Smulders, Havermans, & Jansen, 2004). Impulsivity relates to food intake (Guerrieri et al., 2007; Kane et al., 2004; Nasser, Gluck, & Geliebter, 2004), and is also elevated in obesity (Nederkoorn et al., 2004; Rydén et al., 2003). Restrained eaters are particularly susceptible to overeat (Fedoroff, Polivy, & Herman, 1997), particularly when they are also are also poor inhibitors (Jansen et al., 2009). Hunger, as well, elicits faster (Meule, Lutz, Vögele, & Kübler, 2014) and more uninhibited reactions toward food cues (Loeber, Grosshans, Herpertz, Kiefer, & Herpertz, 2013), highlighting the importance of understanding the influence of internal states on self-control and eating behavior.

Neuroimaging studies have revealed how brain responses to food cues vary between individuals and between internal states in ways that relate to behavior. The response to food cues on fMRI in gustatory and reward regions including the ventral striatum, amygdala and OFC is elevated in individuals with greater reward drive (Beaver et al., 2006), in hungry individuals (Goldstone et al., 2009; Siep et al., 2009) and among obese participants toward high calorie foods (Stoeckel et al., 2008). Functional connectivity between ventral striatum, amygdala, anterior cingulate and premotor cortex has also been found to vary with individual sensitivity to food cues (Passamonti et al., 2009), suggesting that the networks involved in self-control and drive toward food cues change with reward sensitivity. Differences in responses in cortical and subcortical regions have been found to relate to dieting success. Activity on viewing food cues in the ventral striatum and OFC have been shown to predict future weight gain (Demos,

Kelley, & Heatherton, 2011; Yokum, Ng, & Stice, 2011). Dietary restraint has been shown to correlate positively with activation in the dorsal PFC, but negatively with OFC (DelParigi et al., 2007). Dorsolateral PFC activity has further been shown to be greater to in participants who exhibit greater self-control toward food cues than participants who showed poorer self-control. Across groups, activity in this region was found to relate with successful self-control toward food cues by modulating value signals in the ventromedial PFC (Hare, Camerer, & Rangel, 2009). These networks can relate to behavioral outcomes as well. Elevated neural response toward food in the PFC have been shown to predict the likelihood of giving into food temptations in a way that is mediated by ventral striatum has been found to predicts (Lopez et al., 2014). These studies have provided a framework of interacting frontal and subcortical circuitry that underlies successful and unsuccessful self-control of eating behavior.

Dietary restraint is typically impaired under negative emotions, with dieters more frequently failing to exhibit self-control under stress (Heatherton, Herman, & Polivy, 1991; Vohs & Heatherton, 2000). Negative emotions may shift the balance from regulating behavior and giving in to immediate rewards, predisposing some individuals to exhibit increased failures in impulse control (Heatherton & Wagner, 2011). Stress can increase cravings and attention toward food cues (Hepworth, Mogg, Brignell, & Bradley, 2010), and predispose individuals to make unhealthy food choices (O'Connor, Jones, Conner, McMillan, & Ferguson, 2008; D. a Zellner et al., 2006). Dieters are particularly likely to experience food cravings and consume more when experiencing negative emotions (Cools, Schotte, & McNally, 1992; Frost, Goolkasian, Ely, & Blanchard, 1982; Greeno & Wing, 1994; Heatherton et al., 1991; Heatherton, Herman, & Polivy, 1992; Herman & Mack, 1975; Schotte, Cools, & McNally, 1990). Negative

emotions may therefore predispose individuals who are trying to exhibit self-control to more frequent impulse control failures. Indeed, individuals who report higher tendencies for restrained or emotional eating behavior are particularly likely to overeat when experiencing negative emotions (Epel et al., 2001; Oliver et al., 2000; Wallis and Hetherington, 2004; Yeomans and Coughlan, 2009), while others may respond to negative affect by restricting food intake (Macht, 2008), underscoring the importance of examining changes in eating behavior under emotional influences through a lens of individual differences. Self-report measures including the emotional eating scale (Arnow, Kenardy, & Agras, 1995) have provided tools to measure how individual differences in the susceptibility to feel an urge to eat under specific negative emotions relate to the ability to exert self-control. The anxiety subscale of the EES in particular has been shown to predict increased food consumption among in healthy individuals after negative mood induction (Schneider et al., 2012), and poor impulse control (Waller & Osman, 1998).

Negative emotions and stressors also modulate the neural circuitry implicated in behavioral regulation and reward drive, tipping the balance in favor of more unregulated approach behavior. Stress impairs function of the PFC (Arnsten, 2009), while glucocorticoid release sensitizes the reward system to dopamine release by drugs of abuse and food (Adam & Epel, 2007; Covington & Miczek, 2005; Deroche et al., 1995; Piazza & Le Moal, 1998; Sinha, 2001), as well as the cues that predict them (Peciña, Schulkin, & Berridge, 2006). Under stress, dieters show increased activity in the OFC and ventral striatum on fMRI, correlate with subjective experience of stress (Wagner, Boswell, Kelley, & Heatherton, 2012). Sensitization of these regions under negative emotions

therefore provides a neurobiological basis for increased and unregulated approach behavior toward food rewards.

Bulimia nervosa and self-control

Eating disorders affect over 24 million people in the US alone (Fairburn & Harrison, 2003), and have the highest mortality rates of any mental illness (Crow et al., 2009). Bulimia nervosa (BN) is an eating disorder characterized in part by a loss of control over eating behavior resulting in episodes of binge eating (American Psychiatric Association, 2013). Like many psychiatric conditions (Ronald C. Kessler et al., 2005), BN symptoms typically emerge during adolescence. Binge eating behaviors typically begin during mid-adolescence (Stice et al., 1998), with diagnosis for BN reaching its peak in the late teen years (Hudson, Hiripi, Pope, & Kessler, 2007). Patients with BN are typically dissatisfied with their body image (Mohr et al., 2011), and attempt to restrict food intake to manage their weight (Davis, Garner, & Freeman, 1988). After periods of restriction, their self-control mechanisms fail resulting in these characteristic binge episodes. Understanding what drives their failure to exhibit self-control is a key to knowing how to prevent these behaviors from developing and providing appropriate treatments. Explanations have typically posited that an increased sensitivity to food cues (Jansen, 1998), an imbalance between insufficient inhibitory control and enhanced reward drive (Dawe & Loxton, 2004; Wierenga et al., 2014), and an intolerance of negative emotions (Abraham & Beumont, 1982; Heatherton & Baumeister, 1991) are central to binge eating behavior in BN.

Patients with BN typically report less behavioral inhibition (Claes et al., 2005), and an increased sensitivity for rewards (Frank, Reynolds, Shott, & O'Reilly, 2011; Harrison, O'Brien, Lopez, & Treasure, 2010) than healthy

participants on self-report measures. Laboratory studies probing behavior among patients with BN have revealed comparable results. A recent meta-analysis of such studies of showed an small effect for impairment in inhibitory control in patients with BN relative to controls (Wu, Hartmann, Skunde, Herzog, & Friederich, 2013). This effect size increased when stimuli involved food or body imagery (Wu et al., 2013), indicating that "disease-specific" cues are more salient and harder to control responses to for this patient group. Patients with BN show poor performance on the Iowa Gambling Task (Boeka & Lokken, 2006; Liao et al., 2009), suggesting a preference for immediate gratification and greater reward sensitivity. A combination of diminished self-control and greater seeking of rewards may underlie binge eating tendencies in BN (Wierenga et al., 2014).

Exhibiting self-control may be a more inefficient or costly process for this patient population. On a go/nogo task, patients with BN showed increased recruitment of frontal control circuitry during successful response inhibition (Lock, Garrett, Beenhakker, & Reiss, 2011), suggesting an inefficiency to engaging inhibitory control networks. In contrast, fontal circuitry showed reduced activation during more automatic responding (Marsh et al., 2011). Abnormalities of frontostriatal systems involved in moderating reward driven behavior may thus underlie a tendency to see binge eating as rewarding and experience lapses in control over eating behavior (Berner & Marsh, 2014; A. Wagner et al., 2010).

Neural systems involved in evaluating food reward may be altered in patients with BN, as well. Patients with BN typically show an elevated response in the insula and ACC on viewing images of food compared to healthy participants (García-García et al., 2013; Schienle, Schäfer, Hermann, & Vaitl, 2009), although one study showed relatively decreased recruitment of the insula among patients with BN (Brooks et al., 2011). Patients with BN display greater

functional connectivity between the insula and OFC when viewing images of food (Kim, Ku, Lee, Lee, & Jung, 2012), which may underlie a sensitivity for these cues. In contrast, patients with BN show a reduced response to the anticipation and receipt of food rewards in the amygdala, insula and OFC (Bohon & Stice, 2011; G. K. W. Frank et al., 2011), which is enhanced by negative emotions (Bohon & Stice, 2012). This hyporesponsiveness of the reward circuitry may drive patients with BN to seek out food rewards to compensate for a decreased reward response on food intake (Bohon & Stice, 2011).

Binge eating episodes in BN are particularly likely to occur under negative emotions. Increasing negative affect is typically reported in the hours preceding binge episodes (Alpers & Tuschen-Caffier, 2001; Berg et al., 2013; Haedt-Matt & Keel, 2012; Smyth et al., 2007). BN is highly comorbid with mood disorders (Hudson et al., 2007), and patients with BN report rapid mood fluctuations (Johnson & Larson, 1982; Lavender & Anderson, 2010). Patients with BN are less accepting of their own emotions (Svaldi, Griepenstroh, Tuschen-Caffier, & Ehring, 2012), and have limited awareness of their internal emotional states (Sim & Zeman, 2004). With limited emotion regulation strategies (Brockmeyer et al., 2014; Whiteside et al., 2007) patients with BN may be predisposed to engage in binge eating as a maladaptive coping mechanism (Abraham & Beumont, 1982; Vannucci et al., 2015), providing a temporary escape (Heatherton & Baumeister, 1991) or relief from negative emotions (Spoor, Bekker, Van Strien, & van Heck, 2007). Indeed, an elevated urge to act under negative emotions in combination with an expectancy that food will provide relief from negative feelings may underlie the development and maintenance of BN symptoms (Fischer, Peterson, & McCarthy, 2012; Pearson, Wonderlich, & Smith, 2015). It will be valuable,

therefore, to examining how food cues and negative emotions impact self-control behavior in BN to shed light on disordered eating in this patient population.

The Current Thesis

In this thesis, the goal is to further understand how the ability to regulate behavior and its underlying neural circuitry are impacted by varying emotions and cue types across development and in the specific case of BN. We implement a series of go/nogo tasks requiring participants to approach a frequent target ("go") stimulus type and withhold responses from rare non-target ("nogo") stimuli. This paradigm allows us to use erroneous responses on nogo trials, known as commission errors or false alarms, as a measure of inhibitory control failures, and D-prime (*d'*), a composite score of performance across go and nogo trials, as a measure of task performance across changing task demands, referred to as cognitive control (Cohen, Breiner, et al., 2016; Cohen, Dellarco, et al., 2016). By manipulating the content of the stimuli presented as well as the emotional state of the participant, we can use these measures to examine how age and diagnostic group relate to performance on this task. To test how acute emotions affect self-control, we implement an emotional go/nogo paradigm (Hare, Tottenham, Davidson, Glover, & Casey, 2005) under fMRI, where stimuli vary between faces with calm, fear and happy expressions to examine the impact of acute emotions on inhibitory control. We then use a modified version of this task, the cognitive control under emotions (CCUE) task (Cohen, Dellarco, et al., 2016) during which participants perform the task under alternating sustained positive, negative and neutral emotional states. This task allows us to dissociate the impact of sustained and acute emotions on cognitive control, and is performed with fMRI. The third task is a novel go/nogo paradigm contrasting food and non-

food stimuli during these same sustained emotional states. By comparing performance on these task across a sample of healthy controls (HCs) and patients with BN we are able to examine how varying emotions and cues impact performance from late adolescence into early adulthood. This task is then implemented in the fMRI scanner on a group of healthy participants, allowing for the examination of underlying neural circuitry implicated in task performance.

This thesis addresses three questions. In **Chapter 2, "Teens Impulsively React rather than Retreat from Threat,"** (Dreyfuss et al., 2014, *Developmental Neuroscience*), we examine if cues of potential threat impact self-control and it's underlying neural circuitry differently in adolescents relative to adults and children. In **Chapter 3, "Patients with Bulimia Nervosa show Diminished Neurodevelopment of Cognitive Control Under Emotional"** (Dreyfuss et al., under review), we examine if emotional states, brief and prolonged, differentially impact cognitive control in patients with BN and non-eating disordered individuals in late adolescence to adulthood. In **Chapter 4, "Food Cues and Negative Affect Differentially Predict Impulsivity in Typical and Atypical Eating Behaviors,"** (Dreyfuss et al., under review), we examine if the capacity for self-control toward food cues is diminished under emotional states in patients with BN relative to healthy individuals, and if this capacity relates to real-life reports of emotional eating behavior. **Chapter 5, "Developmental and Diagnostic Differences – Conclusions and Implications for Psychiatric Outcomes"** provides a synthesis of the findings across these studies and a discussion of recent findings on circuit development, function and connectivity that may further constrain the conclusions. Finally, we examine limitations of these studies and explore potential future directions for understanding inhibitory and cognitive control across development and psychopathology.

Chapter 2: Teens Impulsively React rather than Retreat from Threat

Introduction

Adolescents commit more crimes per capita than children or adults in the United States (Snyder, 2012) and in nearly all industrialized cultures (Steffensmeier & Allan, 2016). Their proclivity toward incentives (Somerville et al., 2011) and risk taking (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011) has been suggested to underlie the inflection in criminal activity observed during this time. Yet adolescents are better in reasoning and decision-making abilities than children (Reyna & Rivers, 2008) and show less risk taking than adults when outcomes are certain (Tymula et al., 2012). Heightened sensitivity to incentives and risk taking are only part of the equation, as criminal behaviors often involve threatening situations. What happens when adolescents are confronted with a dangerous or threatening situation? Do they retreat or do they react impulsively? The current study tests whether adolescents are more impulsive than adults or children when there is a potential threat using a measure of impulsivity in combination with cues that signal threat (e.g., a frightened face) relative to neutral ones (neutral expressions).

The fight-or-flight response is a physiological reaction to perceived threat (LeDoux, 1998). Fearful faces are a reliable indicator of threat in the immediate environment (F. C. Davis et al., 2011), evoking a well-defined neural response (Sagaspe, Schwartz, & Vuilleumier, 2011; Whalen et al., 1998). Negatively valenced stimuli such as fearful faces generally inhibit behavior, slowing response times and inhibiting motor responses in various tasks (Cohen-Gilbert & Thomas, 2013; Macleod, 1991; Simpson et al., 2000). Adolescents, however, show difficulty suppressing attention and actions toward emotional stimuli even

when irrelevant to the task at hand (Casey et al., 2008; Grose-fifer et al., 2013). This relative lack of cognitive control in the presence of emotional and motivational cues may underlie the behavioral risks that are characteristic of adolescence (Steinberg, 2008).

Prior work suggests that diminished self-control during adolescence may result from competition between limbic and control circuitry (Casey et al., 2008; Ernst, Romeo, & Andersen, 2009; Steinberg, 2008). A combination of evidence from human imaging (Casey et al., 2011; Chugani, Phelps, & Mazziotta, 1987; Galvan et al., 2006; Gogtay et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999), postmortem (Huttenlocher, 1979), and animal (J. Bourgeois & Goldman-rakic, 1994; Rakic, Bourgeois, & Goldman-Rakic, 1994) studies of regional brain changes over the course of development indicate that limbic and prefrontal circuitry interact differentially across development (Hare et al., 2008). Specifically, limbic circuitry is thought to develop earlier than control circuitry as a result of evolutionary pressure and changes in gonad hormone levels that impact limbic structures. This developmental imbalance is suggested to result in a greater influence of limbic than prefrontal regions on behavior during adolescence. This pattern is in contrast to that observed in adulthood, when these circuits have matured or in childhood when they are still developing.

The current study uses a measure of impulsivity in combination with cues that signal threat or safety (fearful or calm facial expressions) to assess developmental changes in emotional responses (i.e., avoidance, approach) to potential threat and their neurobiological bases. First, we test for adolescent-specific responses in brain and behavior when required to suppress responses to threat cues. Second, we explore individual differences in brain activity associated with behavioral performance. Finally, we explore possible sex differences in behavior and brain responses to cues of potential threat.

Methods

Subjects.

Eighty participants between the ages of 6 and 27 were scanned using functional magnetic resonance imaging (fMRI). Data from 23 participants were excluded due to poor overall accuracy (n=9), too much head motion (>2mm translational or 2° rotational motion within a run, n=12), or technical problems n=2) resulting in data from 57 usable subjects (27 females) in all reported analyses. Participants were grouped into child (aged 6–12 years, n=18, 10 male), adolescent (aged 13– 17 years, n=19, 10 male), and adult (18 years or older, n=20, 10 male) age groups. All participants provided informed written consent (parental consent and subject assent for children and adolescents) approved by the Institutional Review Board of Weill Cornell Medical College.

Behavioral Paradigm.

Participants completed six runs of a go-nogo task (Hare et al., 2008; Somerville et al., 2011), using fearful, happy, and calm facial expressions as target (go) and non-target (no-go) stimuli (Figure 2.1A). Further experimental details can be found in previously published work (Hare et al., 2008) that focused on different experimental conditions and analyses than those reported here. Within each run, two types of facial emotions were presented, one serving as the target (go) stimulus, to which they were instructed to press a button, and the other serving as a non-target (nogo) stimulus, for which they were instructed to withhold a button press. Facial expressions were pseudorandomized across the run to control for presentation order, and all combinations of expression were used as both targets and non-targets, resulting in a 2 (Response: go, nogo) x 3 (Emotion: fear, calm, happy) factorial design. Prior to each run, participants were instructed which expression served as the target (go) stimulus, and that they

should respond with a button press only to that expression. Participants were also instructed to respond as fast as possible but to try to avoid making errors. The present report focuses specifically on the analysis of fear nogo trials relative to calm nogo trials, which has not been previously examined or reported (Hare et al., 2008; Somerville et al., 2011).

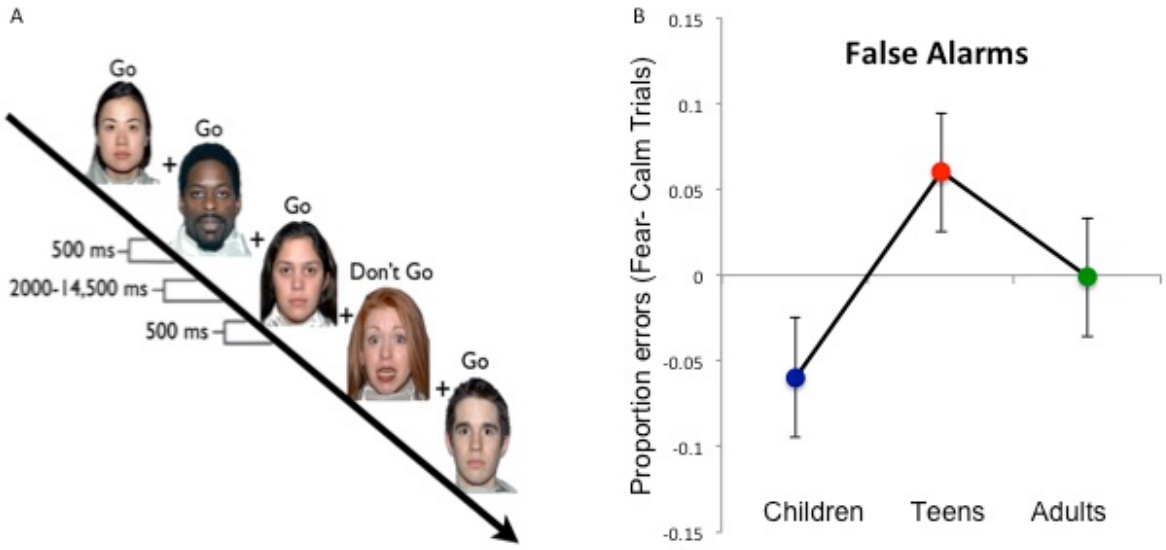

Figure 2.1. Development of impulse control to threat. A) The emotional go/nogo task. B) False alarms (dark gray line) to fear relative to calm nogo trials show an adolescent specific pattern of more commission errors for adolescents than either children ($t_{(35)} = 2.79$, $p < .009$) or adults (: $t_{(37)} = 2.30$, $p < .03$).

Image Acquisition

Participants were scanned with a General Electric Signa 3.0-T fMRI scanner (General Electric Medical Systems, Milwaukee, WI) and quadrature head coil. A high-resolution, T1-weighted anatomical scan (256 X 256 in-plane resolution, 240-mm field of view [FOV], 124 1.5-mm slices) was acquired for each subject for transformation and localization of data to Talairach grid space. A spiral in and out sequence (Glover & Thomason, 2004) was used to acquire

functional imaging data (repetition time = 2500 msec, echo time = 30 msec, FOV = 200 mm, flip angle = 90, skip 0, 64 X 64 matrix). Thirty-four 4-mm-thick coronal slices (3.125 X3.125 mm resolution) covering the entire brain except for the posterior portion of the occipital lobe were acquired per repetition time.

Behavioral Analysis

Behavioral data from the emotional go/nogo task were analyzed for false alarms (incorrect presses to a "nogo" stimulus) to fear and calm cues. Errors were calculated as a difference score between errors to fear nontargets relative to calm nontargets to isolate the effects of negative valence from overall error rate. Error rates were compared between age groups (children, adolescents and adults). A positive value represents a greater proportion of errors to nontarget fear faces than calm faces, while a negative value represents the inverse. Mean reaction times and hit rates have been reported elsewhere (Hare et al., 2008). A two-way ANOVA was performed with age group and sex as the between-subject variables and a difference score between errors to fear nontargets and errors to calm nontargets as the dependent variable of interest.

Imaging Analysis

Imaging data processing and analyses were performed using Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). Functional imaging data were slice-time corrected, realigned within and across runs to correct for head movement, co-registered with each participant's high-resolution anatomical scan, scaled to percent signal change units, and smoothed with a 6mm FWHM Gaussian kernel. A general linear model analysis was performed on each subject to characterize task effects with task regressors (calm–go, calm–nogo, happy–go, happy–nogo, fear–go, fear–nogo, errors), convolved with a gamma-variate

hemodynamic response function. Separate regressors were created for correct go and nogo trials, broken down by emotion (errors were grouped and modeled separately with insufficient numbers to analyze separately). Only correct fear and calm trials were considered of interest and included in the second-level analysis.

We modeled the effects of response (go versus nogo), age group (child, adolescent, or adult), and emotion (fear or calm) on brain activity using a linear mixed-effects model (G. Chen, Saad, Britton, Pine, & Cox, 2013). Parameter estimate (β) maps representing task effects were then transformed into the standard coordinate space of Talairach and Tournoux (1988) by applying the warping parameters obtained from the transformation of each subject's high-resolution anatomical scan. Talairach transformed parameter estimate maps were resampled to a resolution of 3 X 3 X 3mm. A group linear mixed effects model was performed to identify functional regions of interest (ROIs) implicated in the interaction of response, age group and emotion. Imaging findings considered statistically significant exceeded whole-brain correction for multiple comparisons to preserve an alpha < .05 by using a p value/cluster size combination stipulated by Monte Carlo simulations run in the Alphasim program within AFNI. Off-line analyses were conducted in SPSS Statistics 17.0 software (SPSS, Chicago, IL). Beta values were extracted from whole brain corrected ROIs (drawing a 5mm sphere around the peak voxel in each region) and submitted to offline analyses with SPSS (Van Leijenhorst, Zanolie, et al., 2010).

Control Analyses

As task performance was significantly different between age groups, a second set of analyses was conducted to verify that the developmental effects found were not due to lower-level aspects of the data. A second set of first-level GLMs were estimated in which number of correct trials were equated for all

participants across conditions (fear-go, fear-nogo, calm-go, calm-nogo), using the lowest mean number of correct trials of all age groups (calm nogo trials in children; mean = 17). New regressors were generated by randomly selecting 17 trials per condition for inclusion. All other trials were modeled as separate regressors that were not further examined. Beta values were extracted from the 17-trial regressors using the previously defined ROIs, tested for replication, and reported in Results.

Results

Behavioral Results

The two-way ANOVA showed a main effect of age group for false alarms to Fear relative to Calm nontargets, ($F_{(2,59)} = 8.58$, $p < 0.001$), but no main effect of sex ($F_{(1,51)} = .05$, $p > .85$) or interaction with sex ($F_{(2,51)} = .27$, $p > .77$). Post hoc t-tests showed that adolescents made more false alarms to fear nontargets in comparison to calm nontargets than either children ($t_{(35)} = 2.79$, $p < .009$) or adults ($t_{(37)} = 2.30$, $p < .03$) (Figure 2.1B)

.

Imaging Results

The whole-brain age group x response x emotion GLM revealed seven regions of interest (see Table 2.1). Given the behavioral results, the primary regions of interest were those that showed an *adolescent specific* pattern (i.e., greater activity for adolescents relative to children and adults) to fear nontargets relative to calm targets. Two regions showed this pattern: the orbitofrontal cortex and medial prefrontal cortex (Figure 2.2). The striatum showed a similar developmental pattern but post hoc tests between age groups did not reach significance (adolescents vs. children: $p = .09$ and adolescents vs. adults: $p = .11$). Three other regions showed significant age effects for correct fear nogo trials

relative to calm nogo trials. These regions, of the right inferior frontal, right anterior cingulate and left premotor cortices (Figure 2.2), showed an *adolescent emergent* pattern (i.e., greater activity for adolescents and adults relative to children). When controlling for performance differences between age groups by using matched number of trials between age groups (n=17), only the orbitofrontal cortex continued to show the adolescent specific task x age findings previously observed (adolescents vs children: $t_{(35)} = 2.74$, $p < 0.01$ and adolescents vs. adults: $t_{(37)} = 2.27$, $p < 0.03$).

Sex Differences.

We performed exploratory analyses to test for sex differences within the three adolescent-specific findings (i.e., false alarm rates and OFC and mPFC activity to threat nontargets relative to calm nontargets). These exploratory analyses revealed that males rather than females appeared to be driving the inflection in false alarms to threat nontargets during adolescence (Figure 2.3A). Independent t-tests revealed that in males, adolescents made more false alarms than children ($t_{(18)}= 2.28$, $p < .04$) or adults (($t_{(18)}= 2.96$, $p < .009$) and showed a similar pattern in the activation of the OFC, a region implicated in regulation of approach-related behavior (adolescents vs. children: $t_{(18)}= 2.31$, $p < .04$; adolescents vs. adults: $t_{(18)}= 2.39$, $p < .03$, Figure 2.3B).

In contrast, the female age groups did not differ from one another in performance (children vs. adolescents: $p = .44$ and adolescents vs. adults: $p = .07$) or in OFC activity (children vs. adolescents: $p = .19$ and adolescents vs. adults: $p = .76$). Rather, adolescent females showed greater activity in the mPFC, a region implicated in regulation of avoidance related behavior (Figure 2.3C, children vs. adolescents $t_{(15)} = 2.53$, $p < .03$; and adolescents vs. adults (($t_{(17)} =$

2.65, $p < .02$). Males did not differ across age groups in this region (children vs. adolescents: $p = .79$ and adolescents vs. adults: $p = .26$).

Table 2.1. Regions of interest for the interaction of age group X emotion X response type *

No. Voxels	Region	Brodmann's Area	Coordinates (Peak)	F-value
193	R IFG	45	(32 17 18)	8.41
104	L OFC	11	(-38 41 -7)	8.86
78	L mPFC	9	(-8 53 24)	7.95
72	L Premotor	6	(-41 2 7)	8.68
58	L Striatum		(-20 8 -10)	6.59
56	L Motor/Premotor	4, 6	(-14 -8 63)	7.74
51	R ACC	32	(11 2 45)	6.86

* Whole-brain corrected ($p = 0.01$, 47 voxels)

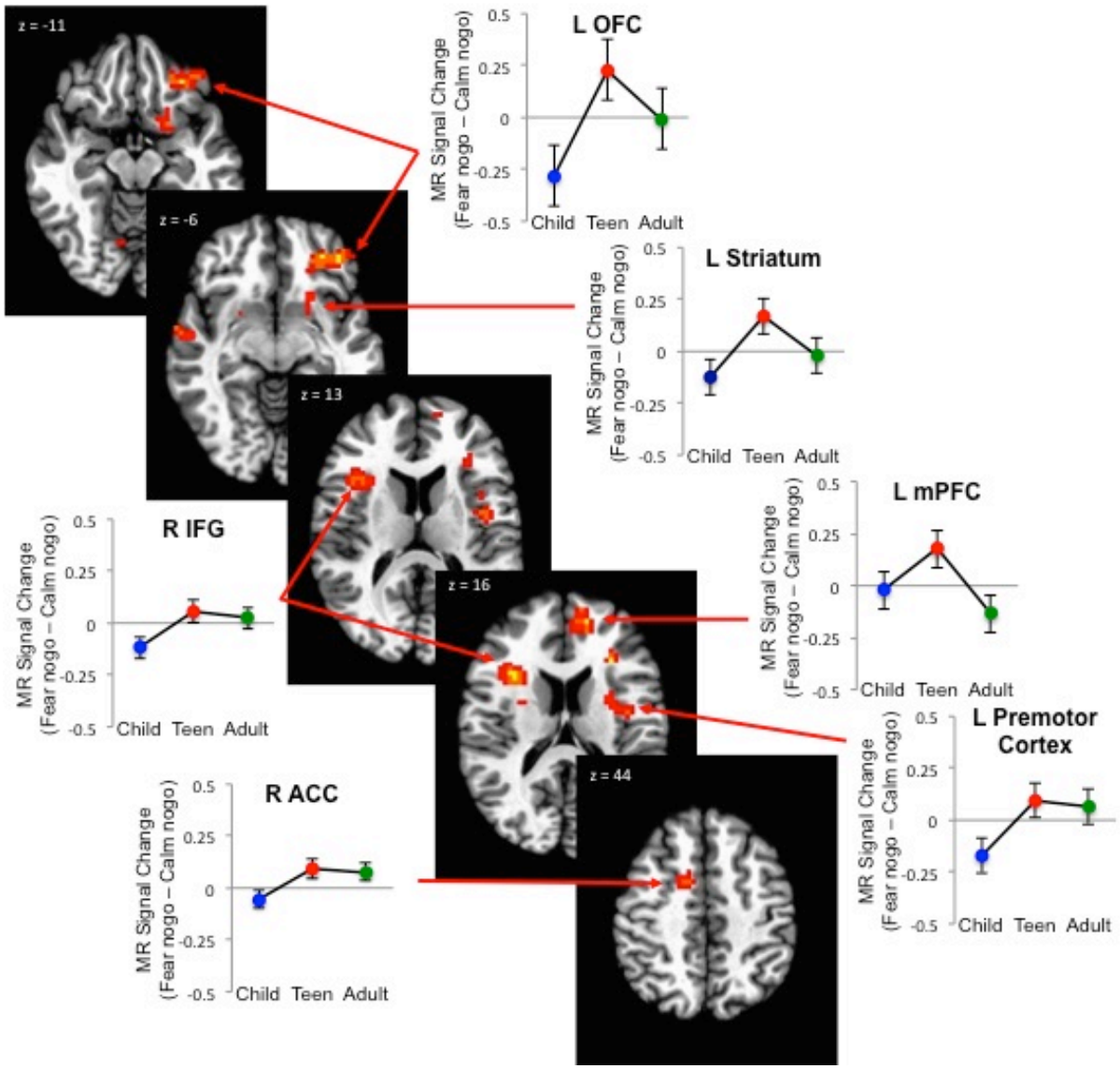

Figure 2.2. Adolescent-specific and adolescent-emergent brain regions. Representative axial images and beta weights for those regions showing an age effect on fear nogo trials relative to calm ones from the whole brain corrected Age (3) X Response (2) X emotion (2) interaction. An adolescent-specific effect on correct fear relative to calm nogo trials was found in contrasts between adolescents relative to children and adults together in the left orbitofrontal cortex (LOFC; $t_{(43)} = 3.11$, $p < .003$) and left medial prefrontal cortex (LmPFC; $t_{(31.06)} = 2.70$, $p < .02$) Adolescent-emergent effects were found in activation contrasts children relative to adolescents and adults together on correct fear relative to calm nogo trials (adolescent emergent) in the right inferior frontal gyrus (RIFG; $t_{(29.15)} = 2.35$, $p < .03$), right anterior cingulate cortex (RACC; $t_{(39.65)} = 2.72$, $p < .01$), and left premotor cortex ($t_{(29.89)} = 2.04$, $p < .05$).

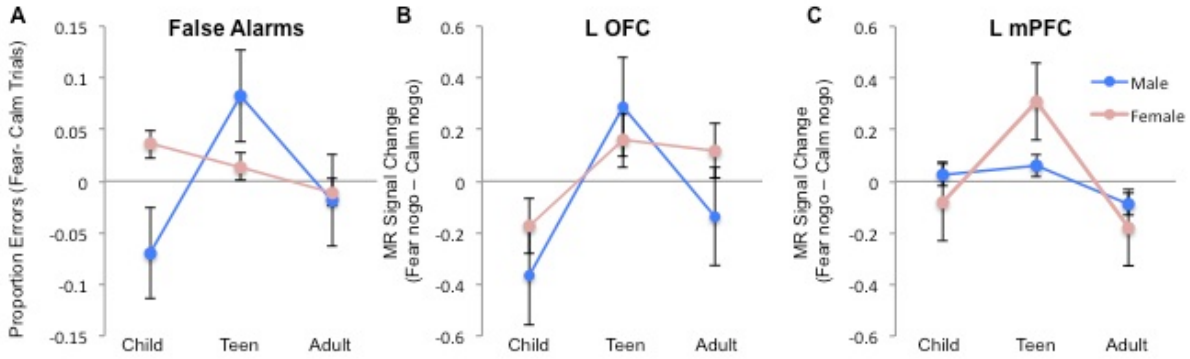

Figure 2.3. Sex Differences in behavior and limbic activity by age group. A) Difference score in number of false alarms to fear nogo trials relative to calm nogo trials by age group and sex; B) Beta weights for orbitofrontal cortex (OFC) to correct fear nogo trials relative to calm nogo trials by age group and sex; and C) Beta weights for mPFC to correct fear nogo trials relative to calm nogo trials by age group and sex.

Discussion

Prior research has focused almost exclusively on how incentives and positive social cues lead to impulsive decisions during adolescence to help explain inflections in risk taking and criminal behavior during this period (Galvan et al., 2006; Somerville et al., 2011; Van Leijenhorst, Zanolie, et al., 2010). The current study examined the effect of threat cues on impulse control and the underlying neural circuitry in adolescents. We found that just as positive cues can lead to more impulsive responses by adolescents relative to children and adults (Somerville et al., 2011), so too can threat cues. This adolescent-specific inflection in false alarms to threat cues was paralleled by marked increases in limbic prefrontal (orbitofrontal and medial prefrontal) regions, implicated in regulating emotional and behavioral responses, particularly in the case of threat-related stimuli.

In contrast to the adolescent specific effects in limbic prefrontal regions, prefrontal control circuitry implicated in detecting and resolving conflict between

two competing responses showed an adolescent emergent pattern (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Casey, Thomas, et al., 2000). Specifically, activity in right inferior frontal gyrus and anterior cingulate cortex increased from childhood to adolescence and then plateaued. These findings are consistent with developmental studies showing that the ability to ignore irrelevant information on cognitive tests like the flanker and go-nogo tasks reaches maturity levels by roughly adolescence (Casey, Thomas, et al., 2000; Enns & Cameron, 1987; Grose-fifer et al., 2013; Passler, Isaac, & Hynd, 1985; Ridderinkhof, van der Molen, Band, & Bashore, 1997).

Adolescents' difficulty in suppressing attention and actions specifically toward negatively valenced information in the current study is a pattern that is emerging in the developmental literature(Cohen-Gilbert & Thomas, 2013; Grose-fifer et al., 2013). This diminished performance is not observed in tasks demanding suppression of attention or actions toward neutral information (Grose-fifer et al., 2013; Somerville et al., 2011). Moreover, recent work suggests that adolescents' actions may be disrupted more easily by negative than positive information (Cohen-Gilbert & Thomas, 2013). Together these findings suggest that nonlinear changes in behavior and limbic circuitry during adolescence may coincide with a heightened sensitivity or pull by emotional cues resulting in the likelihood of approaching, rather than retreating, from potential threat.

Theoretical and empirical accounts for this deflection in performance during adolescence fall along two lines of evidence. The first is evidence of regional brain development with lateral prefrontal cortex continuing to reach structural and functional maturity throughout the adolescent years , and the connections between subcortical and cortical structures continuing to strengthen (Asato et al., 2010; Liston et al., 2006). Given the role of the prefrontal cortex in the regulation of behavior, immature connections between it and subcortical

structures might reduce the capacity to exert cognitive control, particularly in emotionally salient contexts (Casey et al., 2008; Steinberg, 2008). The second line of evidence comes from neuroendocrinology studies, showing an influx of hormones during puberty, thought to sensitize functional properties of certain brain circuits (Ernst et al., 2009; Nelson, Leibenluft, McClure, & Pine, n.d.; Sisk & Zehr, 2005), potentially resulting in adolescent-specific enhanced signaling in regions, such as limbic circuitry, that are especially sensitive to hormonal changes. Thus the heightened recruitment of regulatory prefrontal circuitry when successfully suppressing attention to emotional cues may suggest an adolescent specific hyper-responsiveness to emotional cues that requires greater recruitment of regulatory regions. Together, these observations suggest that diminished regulation of sensitized limbic circuits may heighten the detection of, and response to, salient social cues during adolescence, even when irrelevant for goal-directed behavior.

An elevated sensitivity or reaction to threat cues during adolescence may have important implications for understanding juvenile offenders who commit crimes when in danger or under heightened threat. However, males rather than females commit the majority of juvenile crimes (D'Unger, Land, & McCall, 2002; Poe-Yamagata & Butts, 1996). So how might the adolescent specific behavioral and imaging findings relate to these observed sex differences? Although there was no main effect of, or interaction with sex in the 2 factor ANOVA, exploratory independent t-tests revealed that males rather than females appeared to be driving the inflection in false alarms to threat cues during adolescence. Specifically, male adolescents made more false alarms than either male children or adults and showed a parallel activation pattern in the OFC, a region implicated in regulation of approach-related behavior. In contrast, female adolescents did not significantly differ from female children or adults in their performance or in

activity in this region. Rather, they showed greater activity in the mPFC, a region implicated in regulation of avoidance related behavior. Adolescent males did not significantly differ from children or adults in this region. These exploratory results suggest a possible double dissociation between adolescent males and females in cortical limbic activity related to approaching and avoiding potential threat, respectively that warrants further investigation in a larger sample.

The present study demonstrates that impulsive behavior during adolescence is as likely to occur in the presence of threats as rewards. We show that rather than retreating from threat cues, adolescents are more likely than children or adults to approach them. This developmental pattern is mirrored by adolescent-specific changes in limbic cortical circuitry implicated in detection and assignment of emotional value to inputs and in the subsequent regulation of responses to them (Blakemore, 2008; Nelson & Guyer, 2011; Roy, Shohamy, & Wager, 2012; Somerville et al., 2013). Clearly more research will be required to specify the impact of threat on adolescent behavior. Nonetheless, these findings may have significant implications for policies related to treatment of juvenile offenders who commit their crimes under heightened threat.

Chapter 3: Patients with Bulimia Nervosa show Diminished Neurodevelopment of Cognitive Control Under Emotional

Introduction

The diagnosis of bulimia nervosa (BN) - characterized by episodes of binge eating followed by compensatory behaviors, most commonly purging (APA, 2013) - emerges and peaks in late adolescence (Hudson et al., 2007). Binge eating may be conceptualized as a failure to maintain control over eating behavior following periods of restricted eating, often exhibited by patients with BN to manage their weight (R. J. Davis et al., 1988; P. J. Hay & Claudino, 2010). Binge eating and purging behaviors typically arise in the late teen years (Stice et al., 1998), a time when there is continued development in cognitive control capacity under emotional influences (Cohen et al., 2016a). This developmental period is also a time of continued development of prefrontal circuitry implicated in cognitive and emotional regulation (Gogtay et al., 2004; Silvers et al., 2016). Late adolescence and early adulthood may therefore provide a sensitive window of time for understanding the emergence and maintenance of lapses in self-control implicated in BN psychopathology.

Loss of control over eating behavior in BN often occurs in response to negative emotions. Patients with BN show greater mood fluctuations (Johnson & Larson, 1982), poorer awareness of internal emotional states (Sim & Zeman, 2004), less acceptance of their own emotions (Svaldi et al., 2012) and difficulty in mood regulation (Brockmeyer et al., 2014; Whiteside et al., 2007) relative to healthy controls (HCs). Ecological momentary assessment studies have revealed that negative affect, in particular, tends to increase prior to a binge episode (Berg et al., 2013; Haedt-Matt & Keel, 2012; Smyth et al., 2007). Negative urgency -

the tendency to act more impulsively when experiencing negative emotions - in addition to the expectancy that eating will diminish negative affect have both been associated with BN (Anestis, Smith, Fink, & Joiner, 2009; Hayaki, 2009) and binge eating behaviors (Fischer, Settles, Collins, Gunn, & Smith, 2012). Binge eating may therefore represent a maladaptive coping mechanism providing temporary relief from negative affect, together with a diminished self-control capacity when trying to restrict food intake (Abraham & Beumont, 1982; Heatherton & Baumeister, 1991).

Cognitive control capacity has been tested in patients with BN using laboratory tasks such as the go/nogo, Stroop and stop signal tasks. These cognitive studies have produced mixed results, with a recent meta-analysis showing a small effect of decreased inhibitory control among patients relative to HCs (Wu et al., 2013). However, cognitive control tasks that include motivational cues such as food stimuli (Mobbs, Van der Linden, D'Acremont, & Perroud, 2008) or monetary loss (Rosval et al., 2006) consistently show diminished self-control in patients with BN. These findings suggest that loss of control in BN may be precipitated by reactivity to specific triggers and a sensitivity to rewards and punishments (Jansen, 1998), or an imbalance between reward drive and cognitive control capacity (Wierenga et al., 2014). A fundamental aspect of how individuals experience reward and punishment, especially during adolescence, is through their social interactions. Thus, patients with BN may be particularly sensitive to social cues (e.g., social and emotional facial expressions) associated with positive and negative outcomes.

In the current study, we use the psychophysiologically validated Cognitive Control Under Emotions task (CCUE; Cohen, Dellarco, et al., 2016) together with fMRI to examine how cognitive control and neural processes change under social

and emotional influences from late adolescence into adulthood (18 to 33 years) in patients with BN relative to HCs. This task is a modified go/nogo task that measures the effects of brief vs. sustained negative and positive emotional states on cognitive control capacity. Prior findings from this task indicate that cognitive control, particularly under negative arousal, shows significant continued improvement from the late teen years into the mid-twenties paralleled by enhanced recruitment of prefrontal control circuitry (Cohen, Breiner, et al., 2016). In the current study, we chose an age range for patients and HC participants that would allow us to examine this late development of cognitive control capacity under socioemotional influences and at a time when the diagnosis of BN peaks (Hudson et al., 2007; Stice et al., 1998). We hypothesized that patients with BN would show diminished cognitive control under negative arousal relative to HCs. Given the emergence of BN in late adolescence, we predicted that patients with BN would show diminished improvement in cognitive control capacity with age compared to HCs, particularly under negative emotions. We expected these behavioral patterns would be paralleled by functional differences in prefrontal circuitry implicated in cognitive and emotion regulation.

Methods

Participants

Fifty-two participants completed the study including 22 patients with BN (21 F, ages 18.4-32.8 years, *M*=25.11, *SD*=3.98) and 30 HCs (29 F, ages 18.4-32.1 years, *M*=23.13, *SD*=3.38). Each group included one age-matched (24.1 years-old) male. HCs were recruited from the community via flyers and street fairs, and screened for any personal history of psychiatric or neurologic illness at Weill Cornell Medical College. Twenty-seven of the HC participants were included in two previous studies using this paradigm (Cohen, Breiner, et al.,

2016; Cohen, Dellarco, et al., 2016). The Eating Disorders Research Unit of New York State Psychiatric Institute/Columbia University Medical Center recruited patients with BN, and confirmed the diagnosis by clinical interview and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (First, Spitzer, Gibbon, & Williams, 2002). Patients were further evaluated by the Eating Disorders Examination (Edition 16.0D; Fairburn, Cooper, & Connor, 2008) for frequency of objective bulimic episodes (OBEs) over the preceding 28 days, defined by 1) a loss of control and 2) a large amount eaten. Inclusion criteria were a duration of diagnosis >3 months, engagement in purging via self-induced vomiting, and weight within 80%-160% of ideal body weight (Metropolitain Life Insurance Company, 1959). Exclusion criteria for all participants included any significant medical or neurologic illness, other major Axis I illness, left-handedness and pregnancy. Participants who were on stable doses of antidepressant medication for at least 1 month were not excluded, but participants taking other psychotropic medications were. In addition, all patients were screened for the presence of metal in the body. This study was approved by Institutional Review Boards at both sites, and all participants provided informed consent prior to participation.

Experimental Task

Participants completed six runs of the CCUE task. This adapted emotional go/nogo task consists of brief presentations of socioemotional cues of smiling (happy), fearful and calm (neutral) facial expressions. Participants are instructed to press to a specific target emotion ("go" trial) while withholding responses to other nontarget ("nogo") emotions (Cohen et al., 2016b). The task consists of six runs representing each combination of emotional expression (neutral, fear, happy) as a go or a nogo stimulus. The order of runs was pseudocounterbalanced across participants. To induce sustained states of

emotional arousal, stimuli were superimposed on color backgrounds (teal, purple and yellow), and participants were informed that each color background indicated the possibility of a different outcome. Participants were instructed that an aversive noise ("negative" state) might occur at uncertain intensity and frequency, that a cash reward up to $100 ("positive" state) could occur of uncertain value or that nothing would occur ("neutral" state; Fig 3.1), and that these outcomes would not be related to task performance. The pairing of color background to the 3 different uncontrollable and unpredictable outcomes was counterbalanced across individuals. Each color background occurred twice for 75-seconds during each run of the task. In reality, each individual heard the aversive noise and won a $20 reward exactly once during the task. The negative and positive emotional state manipulation has previously been shown to successfully induce a state of arousal relative to the neutral emotional state based on increased galvanic skin responses and self-report (Cohen, Dellarco, et al., 2016).

Figure 3.1. Schematic of the Cognitive Control Under Emotion (CCUE) task. Participants were instructed to press to a target face emotion and withhold a response to nontarget emotions under different emotionally arousing states. Emotional states were indicated by different colored backgrounds, signaling the possibility that an aversive noise (negative state), cash reward (positive state) or no event (neutral state) would occur.

The experimental task was presented using E-prime 1.0, and projected on a flat screen mounted behind the scanner bore, which was visible to participants via a small mirror placed above the 12-channel head coil. Participants were given a five-button response box and instructed to press the index finger button for go cues. Following task performance, participants were asked whether they expected the reward and the aversive noise during the appropriate color blocks (e.g. “Did you expect to win money more during the purple blocks than the blue or yellow blocks?”). This self-report measure was recorded for only a subset of participants (17 patients and 22 HCs).

fMRI Data Acquisition

Whole-brain MRI data were acquired using a Siemens Magnetom Trio 3.0-T scanner located at the Citigroup Biomedical Imaging Center at Weill Cornell Medical College. A high-resolution T1-weighted magnetization-prepared rapid-acquisition gradient-echo sequence scan was acquired using BIRN optimized sequences (Jovicich et al., 2006; repetition time (TR)=2170 ms, echo time (TE)= 4.33 ms, 256 mm field of view, 160 slices, 1.0 X 1.0 X 1.2 mm sagital slices). Functional images were acquired as 38 echo planar T2*-sensitive pulse sequences covering the full brain each 2500 ms TR (TE=30 ms, 200 mm field of view, 90˚ flip angle, 3.1 X 3.1 X 4.0 mm voxels).

Behavioral analysis

Behavioral data were extracted using Ruby 2.1.0, and analyses were conducted in R version 3.2.4 (R Core Team, 2013). Individual runs of the task were excluded if participants had a proportion of successful go trials (hit rate) below 70%, resulting in removal of 8 runs from 4 HC participants (range: 1-3

runs) and 11 runs from 3 patients (range: 1-5 runs) from analysis. 1 HC participant asked to be removed from the scanner before the final run, so only the 5 runs with usable data were included. Participants with fewer than 3 usable runs (2 patients with BN) and/or commission error rates greater than 2 *SD* above the mean (77.91%, 1 patient, 1 HC) were excluded from all analyses. In addition, data from 2 HCs were excluded due to excessive head motion, defined as >10% of time points censored for >1.56 mm translational or >1˚ rotational motion (Cohen, Breiner, et al., 2016; Cohen, Dellarco, et al., 2016). Forty-six participants were included in the final analyses, consisting of 19 patients with BN (18 F, mean age=25.15, *SD*=4.20) and 27 HCs (26 F, mean age=23.21, *SD*=3.46).

The dependent variable, d-prime *(d'),* takes into account accuracy on both go and nogo trials, used as an index of cognitive control across the changing task demands (Macmillan & Creelman, 2005). D-prime values were calculated as the normalized proportion of incorrect nogo trials (commission error rate) subtracted from the normalized hit rate. To test the hypothesis that patients with BN would show impaired cognitive control behavior toward negative cues and under negative emotional states, *d'* values were entered into a linear mixed effects model using the lme4 package (Bates, Maechler, Bolker, & Walker, 2014) including fixed effects parameters for emotional state (neutral/negative/positive), emotional cue (neutral/fear/happy) and their interaction terms with diagnosis (HC/BN), as well as random effects for participants and random slopes for emotional cues to account for individual sensitivities to different cue types. A significant effect of a factor level or combination of factor levels allows rejection of the null hypothesis that the observed difference in *d'* relative to the baseline levels of the neutral emotional state, neutral face cues and the HC group is due to chance. Subsequently, to test the hypothesis that patients with BN and HCs would show different behavioral trajectories with age, mean-centered age and

the interaction of age by diagnosis were entered into the model and examined as additional explanatory parameters of *d'*. This expanded model was compared to the baseline models using a χ^2 test. A p-value<0.05 on χ^2 test is taken to indicate that the LME with more explanatory parameters explains significantly more variance above and beyond the simpler model. If the parameters do not improve fit with the data, then the simpler model is preferred. To examine if the differential performance with age between patients with BN and HCs was specific to negative emotional cues or states two additional models were run including interactions of age by diagnosis by emotional cue and age by diagnosis by emotional state. These models were then compared for goodness of fit against the model including age by diagnosis.

Self-report data on the believability of the negative and positive emotional arousal manipulations were analyzed by one sample *t*-tests against a response of 1 ("Not at all") across all subjects. Independent samples *t*-tests between patient and HC groups were used to test group differences in believability of the positive and negative outcomes for each background color.

fMRI analysis

Preprocessing and modeling

Preprocessing and analysis of functional imaging data was conducted in AFNI (Cox, 1996). Functional images were subject to slice-time correction, realigned to the initial functional acquisition, and coregistered by six-parameter rigid body transformation to the subject's high-resolution T1 structural image. Normalization was subsequently performed to the MNI 152 1 mm T1 template with 12-parameter affine transformation and nonlinear transformations (*3dQWarp*). Functional images were then resampled to 3 mm isotropic voxel resolution. Signal was smoothed across voxels using a 6 mm FWHM Gaussian

kernel, and signal intensity in each voxel was normalized to percent signal change.

General linear models (GLMs) were run with 16 distinct regressors: 6 regressors for trials on which subjects correctly responded for each combination of emotional cue (neutral/happy/fear) by response type (go/nogo), 3 regressors for sustained emotional states (neutral/positive/negative), 1 regressor for all trials on which subjects failed to respond correctly and 6 regressors to account for both translational and rotational motion. Each trial regressor was convolved with a single-parameter gamma HRF function, while each sustained emotional state regressor was convolved with a block HRF function for the duration of the state. In addition to motion regressors, time points where translational motion >1.56 mm or rotational motion >1˚ relative to the previous frame were excluded from analysis. Subject-level general linear tests (GLTs) were performed to examine BOLD signal during correct trials across emotional cues, sustained emotional state and response type, as well as contrasts with the neutral emotional state for each the positive and negative emotional states, to examine how neural signal relates to behavioral findings.

Group Level Analysis

Group level analyses were performed to examine the neural basis of the two behavioral findings using *3dMEMA*, which takes subject-level beta weights and *t*-statistics as independent variables to account for both within- and across-subject variability (G. Chen, Saad, Nath, Beauchamp, & Cox, 2012). To examine putative differences in cognitive control circuitry, group level analyses were conducted within a mask of prefrontal cortex (Cohen et al, 2016a), defined by regions with ≥50% likelihood of belonging to prefrontal cortex at 1 mm resolution within the Harvard-Oxford cortical structural atlas (Desikan et al., 2006). Given

the behavioral finding that patients with BN showed greater improvement in performance during the positive relative to the neutral emotional state, subject-level GLTs for the contrast of between the positive and neutral emotional states were compared via *t*-test between patients with BN and HCs. To examine the interaction of age by diagnosis on *d'*, subject level GLTs for correct responses across face emotion and response type were entered with a covariate for subject age. Ages were Z-scored across all subjects, and Z-scored ages for patients were multiplied by -1 to account for the interaction effect. A Monte Carlo simulation run via *3dClustSim* within the defined mask with the mean spatial autocorrelation function parameters across subjects indicated that a cluster must consist of at least 10 voxels with a voxel-wise $p < 0.005$ to reject the null hypothesis that the effect observed in a given cluster is due to chance at $\alpha < 0.05$. Only clusters that exceed this threshold are reported. Individual subject regression beta values were extracted from identified regions via *3dmaskave* and subject to offline analyses in R. P-values are reported after being subjected to Bonferroni correction for multiple comparisons.

Results

Task Validation

Participants reported that they expected both the aversive noise ($t(38)=18.649$, $p<0.0001$ and the cash reward ($t(38)=13.33$, $p<0.0001$, $d=1.494$) and, $d=2.360$) to occur during the appropriate blocks of colored backgrounds more than during the other blocks. Patients and HCs did not differ in these expectations for either the aversive noise ($t(31.7)=0.776$, $p=0.444$) or the reward ($t(36.8)=0.669$, $p=0.507$).

Behavioral results

Group differences

The initial model compared *d'* of patients with BN and HCs during sustained positive and negative emotional states relative to a neutral state, and to fearful and happy emotional faces relative to neutral faces. Patients with BN did not differ significantly from HCs in performance during the negative emotional state relative to neutral (β=0.075, p=0.516), but did exhibit greater improvement in performance than HCs during the sustained positive emotional state (β=0.279, p=0.016). There were no significant differences in *d'* between patients and HCs to either emotional cue types relative to neutral ones (fear: β=0.104, p=0.592; happy: β=0.102, p=0.547). Patients with BN showed no significant difference in performance relative to HCs (β =-0.475, p=0.114), when controlling for effects of emotional states and cues.

Developmental differences

Given the development of cognitive control under emotional arousal into the early 20s, we examined if age differentially predicted *d'* between HCs and patients with BN, thus age and the interaction of age by diagnosis were included as explanatory parameters in an expanded model. These additional parameters improved model fit ($\chi^2(2)$=6.648, p=0.036) and showed improvements in *d'* with age among HCs (β=0.100, p=0.009), when controlling for effects of cue and state, and significantly less improvement with age in BN (β=-0.121, p=0.023; Fig. 3.2). To test if these developmental differences in performance were specific to a cue type or emotional state, we examined if the three-way interactions of age by diagnosis by cue and age by diagnosis by emotional state further improved model fit. Neither the three-way interaction with cue ($\chi^2(2)$=6.061, p=0.195), nor the interaction with state ($\chi^2(2)$=4.788, p=0.308) explained significant additional

variance in the data, indicating that the observed developmental differences were not specific to any specific emotional condition.

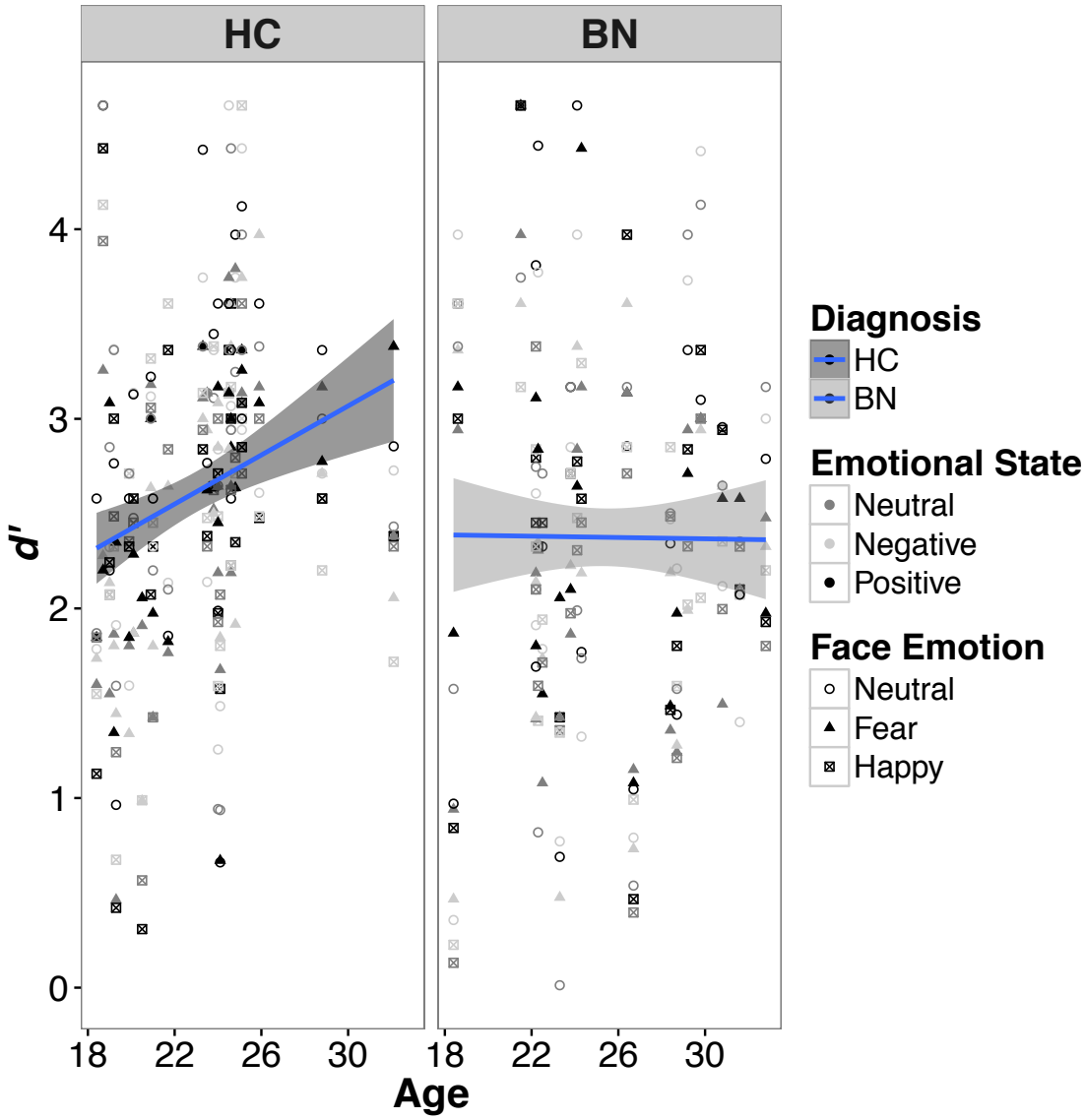

Figure 3.2. Patients with BN fail to show improvement in cognitive control with age. Age predicted improvement in cognitive control as measured by *d'* among healthy control (HC) participants, but not in patients with bulimia nervosa (BN) across cue types (calm, fear and happy facial expression) and neutral, negative (threat of aversive noise) and positive (anticipation of monetary reward) emotional states.

Imaging Results

Building on the developmental behavioral results we tested for an interaction of age by diagnosis in the imaging analyses. Two regions of interest (ROIs), left mid frontal gyrus (x=30.5, y=-45.5, z=15.5, 21 voxels, Z=3.70) and left subgenual cingulate cortex (x=0.5, y=-18.5, z=-11.5, 12 voxels, Z=*3.13*) survived a voxel-wise threshold of p<0.005 and cluster extent ≥10 voxels within the prefrontal cortex (Fig. 3.3). Mean beta weights from these regions were extracted and entered as dependent variables in linear models with diagnostic group, mean-centered age and their interaction as predictors. For HCs, age was associated with increased activity on correct responses in both left mid frontal gyrus (β=0.247, p<0.022) and left subgenual cingulate (β=0.514, p=0.010). Patients with BN showed significantly less activation than HCs in both regions with increasing age (left mid frontal gyrus: β=-0.645, p<0.001; left ACC: β=-1.261, p<0.001).

To examine whether patterns of brain activity in either of these regions was associated with behavioral performance in either group, mixed effects models examined if beta weights predicted *d'*, controlling for effects of emotional cues and states. Within the HC group, mean beta weights during successful task performance significantly predicted *d'* in the left subgenual cingulate cortex(β=0.303, p=0.006) and in left middle frontal gyrus (β=0.247, p=0.027; Fig 3.4). When accounting for age, however, neither the association between mean beta weights and task performance in left ACC (β=0.161, p=0.184) nor in left mid frontal gyrus (β=0.120, p=0.293) remained significant. Among patients with BN, neither left subgenual cingulate (β=-0.105, p=0.601) nor left middle frontal cortex (β=-0.095, p=0.636) predicted *d'*. Thus improvement in performance and increased recruitment of these prefrontal regions in HCs were age-dependent.

Although patients showed improved cognitive control performance during sustained positive affect, no ROIs survived cluster thresholding for whole-brain correction or within the prefrontal cortex for the contrast between patients with BN and HCs for activation during the positive relative to the neutral sustained emotional state.

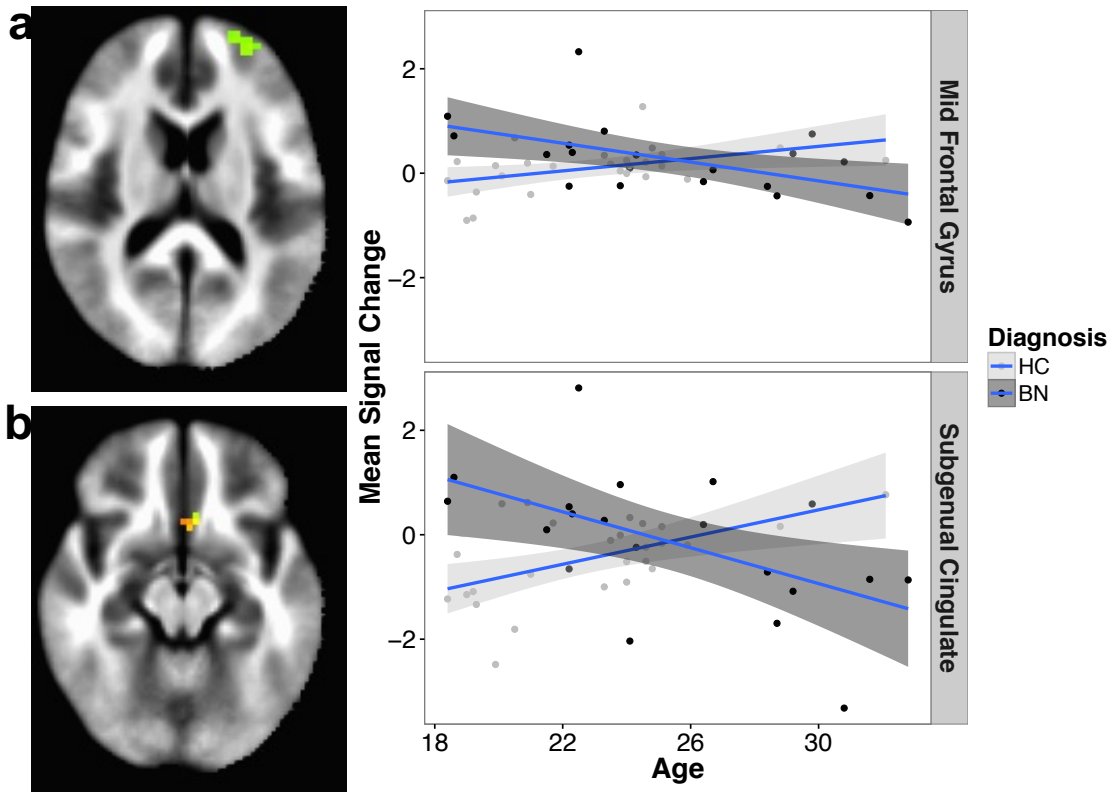

Figure 3.3. Differential recruitment of prefrontal circuitry between diagnostic groups with age. Age predicted increased recruitment of both left mid frontal gyrus (A) and left subgenual cingulate cortex (B) by healthy control (HC) participants, and relatively less regional recruitment among patients with bulimia nervosa (BN) during successful task performance

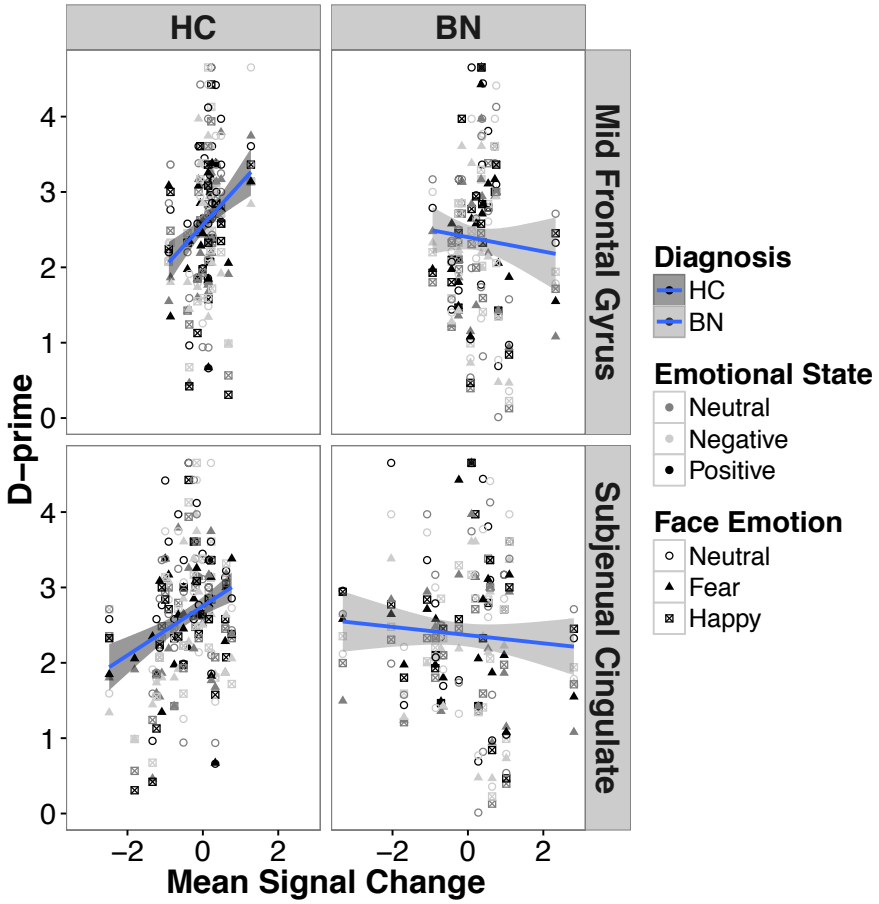

Figure 3.4. **Relationship of activity in subgenual cingulate cortex and mid frontal gyrus with d-prime.** Increased recruitment of subgenual cingulate and mid prefrontal gyrus during successful task performance predicts increased d-prime in healthy control (HC) participants, but not patients with bulimia nervosa (BN), controlling for influences of emotional state and face emotion.

Discussion

The current study tested the hypotheses that patients with BN would exhibit impaired cognitive control under negative emotional arousal relative to HCs that would emerge by late adolescence and persist into adulthood. Cognitive control capacity improved with age from the late teen years into the early thirties for healthy individuals, consistent with previous reports (Cohen et al., 2016a). In contrast, patients with BN showed diminished age-dependent improvement in performance. These divergent behavioral trajectories were

paralleled by distinct patterns of recruitment of prefrontal control circuitry. Specifically, patients with BN did not show enhanced activity in the frontal circuitry that was observed in the HCs during successful task performance. Given the significant development of prefrontal circuitry into the early twenties (Gogtay et al., 2004; Sowell, 2004), and its importance in impulse control and emotion regulation (Cohen, Breiner, et al., 2016; Cohen, Dellarco, et al., 2016; Dreyfuss et al., 2014b; McRae et al., 2012; Somerville et al., 2011) these findings suggest that the emergence and maintenance of BN in late adolescence is associated with altered recruitment of prefrontal control circuitry.

In this study, patients with BN did not differ from HCs in their performance under negative arousal as predicted. The lack of any observed group differences in cognitive control under negative emotional arousal does not indicate that negative affect is not relevant to binge eating behavior in BN. Negative affect has been shown to precede binge episodes more than non-binge meals in patients with BN (Haedt-Matt & Keel, 2012). The negative affect manipulations in the current study may not adequately capture the type or timing of negative affect typically reported in the hours preceding binge eating in BN (Smyth et al., 2007). In this study we used brief and sustained manipulations on the order of milliseconds and minutes rather than hours. Moreover, the negative affect manipulation was associated with a perceived potential threat. This form of negative emotion may differ from the kinds of negative emotions experienced by patients with BN, such as negative self-evaluations (Higgins, Bond, Klein, & Strauman, 1986; Strauman, Vookles, Berenstein, Chaiken, & Higgins, 1991) or guilt (Berg et al., 2013), which have been shown to increase the reward value of food, and drive impulse control failures (Heatherton & Baumeister, 1991; D. D. Wagner et al., 2012). Further examination of different kinds of negative emotions and their impact on cognitive control across development, in combination with the

use of food cues, more specific to eating problem behaviors, may enhance our understanding of the emergence of BN.

Although negative emotions did not influence behavior differentially between patients with BN and HCs, the patient group showed more improvement in cognitive control performance during the positive emotional state than HCs. This effect may in part be associated with HCs' performance being closer to ceiling and, therefore, leaving patients more potential to improve during the positive emotional state. Alternatively, patients with BN may exhibit enhanced cognitive control when experiencing positive emotions. Consistent with this interpretation is prior evidence of patients with BN reporting higher emotional balance and physical well-being when not binging than preceding a binge (Alpers & Tuschen-Caffier, 2001). Binge episodes may therefore be less likely to occur during periods of positive affect. Therapeutic efforts aimed at helping patients' experience and sustain positive affect, in addition to managing negative emotional experiences may provide enhanced treatment responses and/or protection against binge eating.

Our findings should be interpreted in the context of limitations of the current study. First, although age was associated with differences between patients with BN and HCs in the current study, longitudinal data would be needed to show whether individuals with and without BN show different developmental trajectories in cognitive control and neural processes. It would be valuable to examine how cognitive control and neural circuitry at younger ages may predict the onset of BN. An additional limitation is that while patients with BN and HCs in the current study covered the same age ranges, participants were not age-matched between groups, and therefore inferences from these findings warrant replication. The findings of this study would also be strengthened with a

comparison diagnostic group to show whether the findings are specific to BN or are related to a more general class of psychopathologies. Certain traits that may relate to cognitive control behavior, such as high negative urgency, are not specific features of BN, but may function in conjunction with the expectancy that eating will relieve negative emotions in developing and reinforcing BN symptoms (Fischer, Settles, et al., 2012). Examining psychopathologies by dimensional measures such as these rather than categorically by diagnosis has the potential to reveal common and unique characterizations of different diagnostic groups and how they emerge across development (Casey, Oliveri, & Insel, 2014).

Alternative explanations for the results should also be considered. It may be the case that the patients who fail to show improvements in cognitive control are the most likely to remain symptomatic into adulthood. As most patients are diagnosed during late adolescence or early adulthood, time since diagnosis and age are highly correlated. Distinguishing between risk-factors for disease onset and disease maintenance warrants further study with impulse control paradigms.

The findings presented in the current study highlight the importance of a neurodevelopmental approach in understanding the psychopathology of BN. Patients with BN may fail to show developmental changes in prefrontal neurocircuitry crucial for maintaining self-control. This altered development may in turn make them more susceptible to failures in behavioral control (e.g., binge eating). Studying how this circuitry differs between recovered patients with BN and patients who remain symptomatic may reveal how improvements in cognitive control and its underlying neural circuitry relate to symptomatology. Moreover, our findings have implications for treatment in that the capacity for and stability of positive affect may be valuable in enhancing cognitive control in patients with BN. Thus, cognitive behavioral interventions that emphasize positive emotions for treating as well as potentially protecting at risk populations from bingeing

behaviors may have utility. In sum, examining BN from the perspective of a neurodevelopmental framework may be crucial for understanding the onset and maintenance of eating-disordered psychopathology as well as its prevention.

Chapter 4: Food Cues and Negative Affect Differentially Predict Impulsivity in Typical and Atypical Eating Behaviors

Introduction

Emotional stress can lead people to overeat as a means to provide quick relief from negative feelings, often at the cost of disrupting long-term health and dietary goals. Stress and negative affect can impact self-control and trigger disinhibited eating (Greeno & Wing, 1994), although this effect varies across individuals (Michael Macht, 2008). Restrained and emotional eaters are particularly likely to overeat when confronted with appetizing cues (Fedoroff et al., 1997; Rogers & Hill, 1989), or under negative emotional arousal (Herman & Mack, 1975; Oliver et al., 2000; Wallis & Hetherington, 2004). At the pathological extreme, a heightened sensitivity to food cues (Jansen, 1998; Schienle et al., 2009; Staiger, Dawe, & McCarthy, 2000; Van den Eynde et al., 2012), deficient inhibitory control (Wierenga et al., 2014) and negative affect (Heatherton & Baumeister, 1991; Polivy & Herman, 1993) have been proposed as precipitating factors for binge eating behavior. This extreme loss of control over eating behavior is integral to several eating disorders including bulimia nervosa (BN; American Psychiatric Association, 2013) and the focus of the current study. Specifically, how does emotional arousal impact inhibitory control to food cues and how does it relate to problem eating behaviors?

A number of neuropsychological studies have examined the role of deficient inhibitory control in BN. The literature comparing patients with BN and HCs on tasks measuring self-control have yielded mixed results. For example, although a meta-analysis of Stroop tasks showed a medium effect size of greater attentional bias toward food cues among patients with BN relative to HCs (S. Brooks, Prince, Stahl, Campbell, & Treasure, 2011), go/nogo studies have failed

to show any effect at all, or only a trend of diminished control among patients with BN (Lock et al., 2011; Rosval et al., 2006). A more recent meta-analysis of 24 studies revealed a small effect size of diminished cognitive control in patients with a modest effect size when the cues were food stimuli (Wu et al., 2013). Whether patients with BN are generally deficient in inhibitory control remains unclear. However, the findings suggest that food cues may have a particular attentional draw and diminish cognitive control or increase approach-related behavior in patients with BN (Mobbs et al., 2008). The current study examines this further by using food cues in a go/nogo task.

Another precipitating factor for binge eating that has been examined is that of negative emotional arousal. Patients with BN report inferior interoceptive awareness of their own emotional states (Sim & Zeman, 2004), frequent mood fluctuations (Johnson & Larson, 1982), and difficulty in mood regulation (Brockmeyer et al., 2014; Whiteside et al., 2007). These emotional factors along with an urge to act when distressed (Claes et al., 2005; Fischer, Smith, & Anderson, 2003) and an expectation that eating can provide relief from negative affect (Hayaki, 2009; Hohlstein, Smith, & Atlas, 1998) may render patients with BN susceptible toward impulsive actions, particularly eating, under negative emotional stress (Heatherton & Wagner, 2011; Pearson et al., 2015). Indeed, patients with BN engage in higher rates of binge eating following steady increases in negative affect (Alpers & Tuschen-Caffier, 2001; Crosby et al., 2009; Smyth et al., 2007). How negative emotions impact impulse control, especially toward food cues, remains relatively unexplored, and is the focus of the current study.

A key question in understanding how these factors may lead to episodes of binge eating is whether food cues and emotional states have dissociable effects on impulsivity in individuals with and without BN. A variant of a go/nogo

task referred to as the Food and Emotional Arousal Task (FEAST), was developed to address this question. This task uses food and non-food cues alternatively as targets ("gos") or non-targets ("nogos"), building on our prior work showing that food cues lead to higher mean commission errors than non-food cues (Teslovich, Freidl, et al., 2014). To test the effects of negative emotional states on impulse control, participants completed this task during previously validated experimental manipulations of emotionally arousing states (Cohen, Dellarco, et al., 2016). To capture the negative affective state of stress and worry, we used a manipulation of sustained anticipation of an unpredictable and uncontrollable negative event. Control conditions were included to test the specificity of negative affect on impulsivity to food cues.

The impact of emotional arousal on eating behavior varies across individuals with some individuals eating more and others eating less (Michael Macht, 2008). In the current study, variation in emotional eating behavior was measured with the Emotional Eating Scale (EES; Arnow, Kenardy, & Agras, 1995), the only validated self-report of emotional eating problem behavior. To parallel our experimental manipulation of sustained anticipation of an unpredictable negative event we focused on the EES anxiety subscale. We hypothesized that: 1) patients with BN would make more commission errors specifically toward food cues and especially during the negative emotional state; and 2) EES anxiety would relate to increased commission errors toward food cues during the negative emotional state.

Methods

Participants

HCs were recruited and screened for any personal history of psychiatric or neurologic illness at Weill Cornell Medical College. Exclusion criteria included

any significant medical or neurologic illness, pregnancy or other major Axis I illness. Patients with BN were recruited through the Eating Disorders Research Unit of New York State Psychiatric Institute/Columbia University Medical Center. The diagnosis of BN was confirmed by clinical interview and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (First et al., 2002). Participants with BN were included if they had a duration of diagnosis>3 months, and were within 80%-160% of ideal body weight (Metropolitain Life Insurance Company, 1959). Only patients who engaged in self-induced vomiting were included for homogeneity between patients. Frequency of binge eating was assessed by objective bulimic episodes (OBEs) over the previous 28 days via the Eating Disorders Examination (Edition 16.0D) (Fairburn et al., 2008). OBEs were defined as episodes involving 1) a loss of control and 2) a large amount eaten. Patients with moderate level depressive and anxiety disorders were not excluded. Participants who were on stable doses of antidepressant medication for at least 1 month were not excluded, but participants taking other psychiatric medications were.

Twenty-six patients with BN (25 females) and 36 HCs (29 females) 18-33 years-old were recruited to participate in this study including one male patient, for which an age-matched HC male was included for analysis. Final participant groups were comparable in age (HC: *M*=24.2, *SD*=3.5; BN: *M*=24.6, *SD*=3.7). This study was approved by Institutional Review Boards at both sites and all participants provided written informed consent prior to participation.

FEAST Paradigm

Stimuli consisted of a validated set of pictures of 10 high-calorie (>350 Cal/100g), 10 low-calorie (<200 Cal/100g) and 20 non-food objects (Teslovich, Freidl, et al., 2014). High- and low-calorie food items were composed of an equal number of savory and sweet items. Prior to inclusion, 23 independent reviewers

rated items on 7-point Likert scales assessing if items were exciting, familiar, pretty, common and yummy (foods only). Items were excluded if their mean ratings were “strange” (≤2), “unfamiliar”, “unexciting” or “not pretty” (≥5), or “not yummy” (≥3). Cronbach’s alpha was used as a measure of inter-rater reliability as in Teslovich *et al.* 2014, and reported in Supplemental Table 1.

The go/nogo task was administered using E-Prime 2.0 presentation software (Psychology Software Tools, Inc. Pittsburg, PA). Participants were instructed to press to a target (“go”) cue type, which appeared in 74% of trials, to develop a pre-potent response to that cue type, while the other 26% of trials were composed of non-target (“nogo”) stimuli. The task consisted of 6 runs, with food and non-food object cue types counterbalanced as targets and non-targets. Each cue appeared as a target 342 times, and as a non-target 90 times. The order of runs was pseudorandomized across participants. Stimuli appeared for 500 ms with 1500 ms interstimulus intervals between presentations (Fig. 4.1). Responses were recorded for the full 2 s.

Stimuli were overlaid on yellow, blue and purple color backgrounds to indicate distinct emotional state manipulations that represented the possibility of hearing an aversive noise (“negative”), winning up to $100 (control “positive” state), or no event occurring (“neutral” state). Participants were informed that the possibility of an event occurring was not related to their performance, to simulate both unpredictable and uncontrollable acute stress. Each background color occurred twice during each of 6 runs for 1 minute each (total of 12 minutes). The pairing of color background to potential outcomes was pseudorandomized between participants and a practice session occurred prior to participating to ensure understanding of the task conditions.

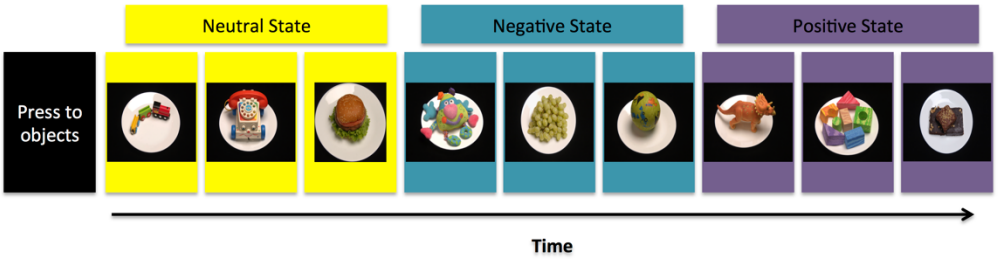

Figure 4.1. Schematic of one run of the experimental paradigm with objects cues as targets (go) and food cues as rare non-targets (nogo). Cues are superimposed on color backgrounds evoking negative (potential aversive noise), positive (potential reward) or neutral (no event) emotional states.

Self-Report Questionnaires

Following testing, participants were given a post-test questionnaire to indicate whether any of the food stimuli were foods they would not eat. Twenty-four of the 26 patients with BN and all HCs also rated how strongly they associated the negative and positive outcomes with the appropriate background color, how hungry they were before and after completing the task, and rated each stimulus on "how much do you like this image?" on a seven-point Likert scale (1="not at all"; 7="very much"). Two patients with BN failed to complete this survey.

All participants completed the Emotional Eating Scale (EES; Arnow *et al.* 1995), on which they rated how much emotions increase their desire to eat on a 5-point Likert scale. These ratings composed distinct subscales of susceptibility to eat under emotional states of anxiety, anger and depression. In the current study we focused on the anxiety subscale that paralleled our negative arousal experimental manipulation.

Statistical Analyses

To test the validity of the emotional state manipulation, self-report of believability of emotional states were analyzed by one sample t-test across all participants against a response of 1 ("not at all"), and between patients with BN and HCs by independent samples t-test. Reported hunger levels before and after the task were analyzed via a repeated measures analysis of variance (rANOVA) to test the main effects of diagnosis (HC/BN), time point (before/after) and their interaction. Finally, each participant's average liking ratings for objects and for foods that participants reported they would eat were analyzed via rANOVA with main effects for diagnosis, cue type and their interaction. Post-hoc t-tests were performed on significant effects from each rANOVA.

Responses of the anxiety subscale of the EES were adjusted to a 100-point scale for each participant, and compared between groups by an independent samples t-test. To probe how disease behavior related to self-reported anxious eating, a correlation was performed between EES anxiety and OBEs per 28 days among patients.

Commission error rates were computed as the proportion of nogo trials on which the participant erroneously responded to a rare non-target (food, object) within each emotional state (neutral, negative, positive). Trials with reaction times (RTs) <100 ms (n=29 trials), and trials representing food cues that participants reported they would never eat were excluded from analysis (HC: M=1.85, SD=2.37 cues, BN: mean=3.65 SD=3.76 cues). Linear mixed effect models (LMEs) were run using the lme4 package (Bates et al., 2014) in R version 3.0.2 (R Core Team, 2013) to test the main hypotheses that: (1) patients with BN would have greater commission error rates specifically toward food cues, which would be enhanced during the negative emotional state, and (2) self-reported anxious eating behavior would be associated with greater commission error rates

during the negative emotional state. For the first hypothesis, commission error rates were entered as dependent variables in LMEs with fixed effects for diagnosis, cue type (object/food), emotional state (neutral/negative/positive), and their interaction terms as fixed effects factors. To examine the second hypothesis, the interaction of emotional state (neutral/negative/positive) and mean-centered and scaled EES anxiety were entered into distinct LMEs predicting commission error rates toward food and non-food object cues by HCs. Patient commission error rates were then examined as a function of EES anxiety to test if patient variability in EES anxiety predicted commission error rates during the negative emotional state as found in HCs. All models included subjects as random effects. Categorical factors in these models were each assigned baseline levels: HC for diagnostic group and neutral for emotional state. A significant effect of another factor level allows rejection of the null hypothesis that the predicted change in commission error rates of that factor level relative to the baseline level is due to chance.

Results

Validation of FEAST paradigm

Liking ratings showed a main effect of cue type ($F_{(1, 62)}$=166.64, p<0.001, η_p^2=0.73) with participants liking food more than non-food cues ($t_{(63)}$=12.96, p<0.001, d=2.18). There was no effect of diagnostic group ($F_{(1,62)=}$0.95, p>0.250, η_p^2=0.02) nor interaction of diagnosis by cue type ($F_{(1,62)}$=0.50, p>0.250, η_p^2=0.01) on liking ratings. An rANCOVA of hunger ratings revealed a main effect for time ($F_{(1,47)}$=32.158, p<0.001, η_p^2=0.39), such that reported hunger was greater by the end of the task ($t_{(101)}$=3.3, p<0.002, d=0.65). Patients and HCs did not differ in reported hunger ($F_{(1,15)}$=2.064, p=0.157, η_p^2=0.04), nor was there was an interaction of diagnosis by time point ($F_{(1,2)}$=1.096, p>0.250, η_p^2=0.02),

indicating that groups did not differ in how much their hunger levels increased. One sample t-tests of the effectiveness of the emotional state manipulation indicated that participants expected the aversive noise ($t_{(52)}$=25.91, p<0.001, d=7.19) and the reward ($t_{(53)}$=24.69, p<0.001, d=6.78) to occur during the appropriate color backgrounds. Independent t-tests revealed no significant differences between patients and HCs in expectation of either the negative ($t_{(32.13)}$=-1.56, p=0.13) or positive ($t_{(47.36)}$=0.69, p>0.250) outcome with the appropriate background colors.

Self-Report Measures

Patients scored higher (M=62.31, SD=16.1) than HCs (M=38.67, SD=11.85) on the anxiety subscale of the EES ($t_{(45.21)}$=6.15, p<0.001, d=1.83), consistent with the emotional eating literature linking this behavior with risk for eating disorders. Emotional eating ratings were positively correlated with frequency of binge eating behavior in patients with BN, as measured by OBEs over the most recent 28-day period ($r_{(24)}$=0.47, p=0.037; Fig 4.2).

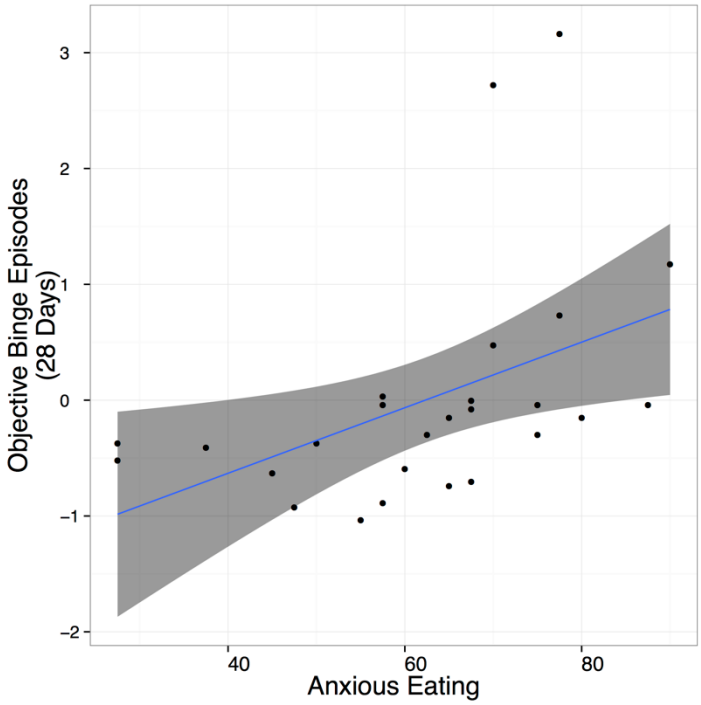

Figure 4.2. Relationship between anxious eating tendency and binge eating frequency. Increased anxious eating as reported on the emotional eating scale correlated positively with frequency of objective binge episodes during the 28 days prior to clinical interview.

Mean commission error rates

A diagnosis of BN predicted increased commission error rates relative to controls specifically toward food cues (β=0.12, p=0.017), but not nonfood objects (β=0.03, p>0.250; Fig. 4.3). Emotional states did not predict different commission error rates between patients with BN and HCs to objects (negative: β=0.01, p=0.82; positive: β=-0.01, p>0.250) or to food cues (negative: β=-0.04, p>0.250; positive: β=-0.03, p>0.250).

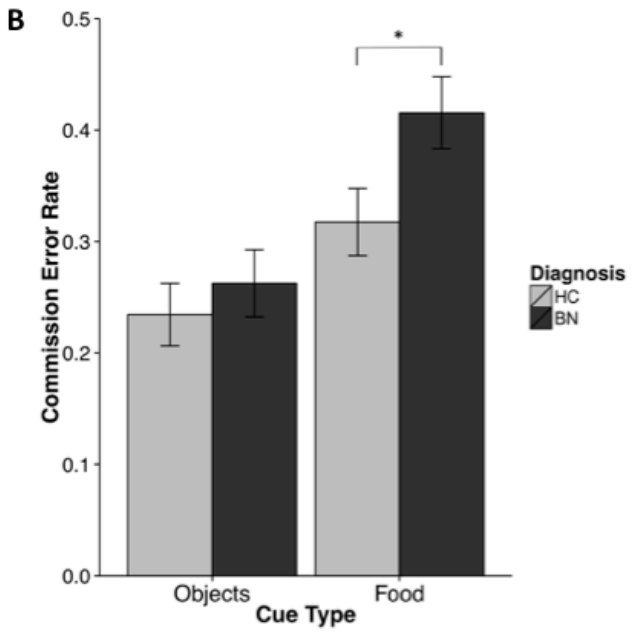

Figure 4.3. Commission error rates by cue type and diagnosis. Patients with bulimia nervosa (BN) exhibited enhanced commission error rates were specifically enhanced toward food cue non-targets, not objects.

Association between commission errors and emotional eating

Increasing EES anxiety in HCs predicted greater commission error rates to food cues in the negative (β=0.06, p=0.017; Fig. 4.4), but not in the positive (β=0.02, p>0.250) emotional state relative to the neutral condition. EES anxiety ratings were not significantly associated with commission error rates to non-food objects under either the negative (β=0.03, p=0.214) or positive (β=0.03, p=0.179) arousal states. Patients with BN did not show an association between EES anxiety ratings and commission errors to either cue type in the negative (food: β=-0.01, p>0.250; objects: β=0.01, p>0.250) or positive (food: β=0.04, p=0.156; objects: β<0.01, p>0.250) emotional states relative to the neutral state condition.

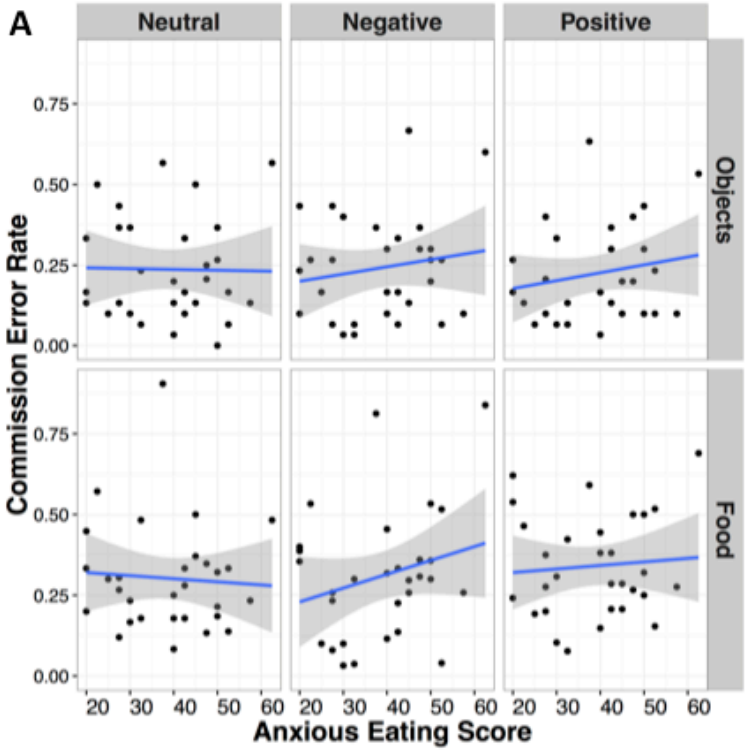

Figure 4.4. Commission error rates by anxious eating rating. Anxiety subscale of the Emotional Eating Scale correlated with commission error rates toward food cues during the negative relative to neutral emotional state in healthy controls (HCs).

Discussion

The current study examined whether typical and pathological forms of problem eating behavior were differentially associated with poor impulse control to food cues under negative emotional states of arousal. Patients with BN were more impulsive to food cues than healthy controls, regardless of emotional state. A diagnosis of BN was associated also with higher rates of anxious eating that was positively associated with frequency of binge episodes. The impact of negative emotional state on impulsivity to food cues was related to emotional

eating only in healthy individuals. These findings suggest a possible dissociation between factors that drive impulsivity in patients with BN and HCs, and highlight possible differences in triggers of pathological versus non-pathological eating problem behavior.

Although patients with BN did not show an increase in commission error rates to food cues during the negative emotional state, the role of negative affect in BN should not be underplayed. The intensity or type of negative affect induced by the threat of an unpredictable and uncontrollable aversive event employed in the present study may be qualitatively different from that which elicits binge eating in BN. Negative mood states that precede binging episodes in BN may be more related to negative self-evaluation compared to an assumed ideal standard (Stephen A. Wonderlich et al., 2008), or feelings of guilt (Berg et al., 2013). The short duration of emotional states in the current study may not have been sufficiently long to elicit the impulse control failures related to more prolonged periods of negative affect that typically precede a binge episode (Smyth et al., 2007). Additionally, binge eating may involve failures in multiple domains of inhibitory control. While food cues may increase the likelihood of impulse control failures in BN, prolonged periods of negative affect may be critical in allowing eating to proceed unregulated during a binge episode. Indeed, binge eating tends to occur during periods of greater negative affect than non-binge meals in patients with BN (Haedt-Matt & Keel, 2012), implicating negative affect more in the dysregulation rather than the onset of eating behavior. In the present study, we specifically tested how approach behavior is modulated by cue type and affective state, but the kind of inhibitory control required to stop eating at a point of satiety rather than progressing to a binge may not be observable in the momentary lapses in self-control measured here.

Our task was able to dissociate valence and arousal to show a valence-specific effect on impulsivity to food cues in healthy individuals that was associated with problem eating behavior. Specifically, the anxiety subscale of the EES predicted an increase in commission error rates specifically to food cues in the negative emotional state relative to the positive or neutral state in healthy individuals. These individual differences in emotional eating and impulsivity are consistent with observations that negative emotions have variable effects on eating behavior (Michael Macht, 2008).

Patients with BN rated themselves higher on the EES anxiety subscale than HCs, and EES anxiety scores correlated with binge eating behavior among the patient group, This association is consistent with previous reports (Fioravanti et al., 2014; Ricca et al., 2012; Rotella et al., 2013) and provides further support for a role of anxiety in dysregulated patterns of eating behavior in BN. The lack of an association between self-reported emotional eating and commission error rates to food cues during the negative emotional state in individuals with BN may have been due to little overlap in distributions of scores between patients and HCs, such that increases in EES anxiety did not predict increased commission error rates in the higher range of scores typically reported by patients. The current study focused on experimental manipulations and self-report measures of anxiety. Although patients with BN report that anxiety increases their desire to eat, they do not report greater anxiety just prior to binge episodes (Alpers & Tuschen-Caffier, 2001). Future studies are needed to elucidate the role of anxiety in inhibitory control failures and binge eating specific to BN. Limitations of the current study should be considered when interpreting the findings. First, the relatively small sample sizes within patient and HC groups may have underpowered the study to detect effects of the negative emotional state manipulation. Moreover, using only self-report of emotional states rather than

objective psychophysiological measures of arousal during emotional states may have underestimated differences in levels of emotional arousal between groups. Additionally, while there were no differences in hunger ratings, participants were not required to restrict food to the same degree before participating in the study. How much a subject's performance was influenced by state of satiety or hunger could therefore have been variable.

In the current study, we show that reactivity to food cues leads to increases in impulsive tendencies among patients with BN. In contrast, impulsivity when anticipating a negative event is associated with individual differences in self-reported emotional eating among HCs, not observed in BN. Together, our findings highlight the importance of both dimensional and diagnostic measures in our understanding of how food cues and negative affect can diminish self-control and lead to problem eating behaviors, both pathological and typical.

Limitations of the current study should be considered when interpreting the findings. First, the relatively small sample sizes within patient and HC groups may have underpowered the study to detect effects of the negative emotional state manipulation. Moreover, using only self-report of emotional states rather than objective psychophysiological measures of arousal during emotional states may have underestimated differences in levels of emotional arousal between groups. Additionally, while there were no differences in hunger ratings, participants were not required to restrict food to the same degree before participating in the study. How much a subject's performance was influenced by state of satiety or hunger could therefore have been variable.

In the current study, we show that reactivity to food cues leads to increases in impulsive tendencies among patients with BN. In contrast, impulsivity when anticipating a negative event is associated with individual

differences in self-reported emotional eating among HCs, not observed in BN. Together, our findings highlight the importance of both dimensional and diagnostic measures in our understanding of how food cues and negative affect can diminish self-control and lead to problem eating behaviors, both pathological and typical.

Chapter 5: Developmental and Diagnostic Differences – Conclusions and Implications for Psychiatric Outcomes

Introductions

Everyone experiences lapses in self-control. Which environmental and emotional influences are most likely to impair an individual's ability to exert self-control varies across development, between individuals and by diagnostic group. The capacity to exhibit self-control emerges over the course of development (Luna, Garver, Urban, Lazar, & Sweeney, 2004), but during adolescence in particular it is more sensitive to disruption by salient emotional cues in the environment (Somerville et al., 2011; Van Leijenhorst, Moor, et al., 2010). This is a particularly crucial time period to examine because it is a peak period for the onset of psychopathology (Ronald C. Kessler et al., 2005), including disorders characterized by diminished impulse control like BN. In the current thesis, we used three variants of a go/nogo paradigm to examine how inhibitory control is impacted by appetitive and aversive cues and states across development, between individuals and between eating disorder and non-eating disordered groups. In Chapter 2, we asked whether teens were reactive to aversive social cues of potential threat, and probed the neural circuitry underlying these behavioral patterns. In Chapter 3, we examined how cognitive control and underlying neural systems developed from early adolescence into adulthood among patients with BN relative to HCs under changing emotional conditions. In Chapter 4, we explored how individual differences in eating behavior and a diagnosis of BN predicted impulse control failures toward appetitive food cues under negative, positive and neutral emotional states. In this final chapter, I integrate these findings within the context of a recent study examining the relationship between functional connectivity of subcortical and prefrontal systems

and inhibitory control, discuss limitations of the methods used, speculate on future directions and provide potential implications of the findings for treatment and prevention of psychopathology and poor decision making during adolescence.

Self-control circuitry and inhibitor control to emotional cues

In **Chapter 2, "Teens Impulsively React rather than Retreat from Threat,"** we found that teens were more likely than adults or children to make false alarms to cues of potential threat relative to neutral social cues (Figure 2.1). This behavioral finding was paralleled by increased activity when successfully withholding response to fear faces compared to calm faces in left OFG and mPFC, with a similar but non-significant pattern observed in the left striatum (Figure 2.2). Heightened responses in these regions implicated in regulating emotional, behavioral and reward drive may suggest a hyper-responsiveness to emotional cues among adolescents, requiring greater recruitment for successful response suppression.

Beyond the regional changes as found in this study, connectivity between networks changes over the course of development between subcortical (Fareri et al., 2015), and between subcortical and cortical networks (Gabard-Durnam et al., 2014), which have implications for emotional regulation success (H. Lee et al., 2012). Additionally, the amygdala is implicated in promoting motivational behavior via glutamatergic projections to the ventral striatum (Stuber et al., 2011). The connections between these structures mature at different rates (Asato et al., 2010; Bouwmeester, Smits, & Van Ree, 2002; Fareri et al., 2015; Swartz et al., 2014), suggesting that increasing age may relate to changes in functional connectivity between the amygdala, ventral striatum and PFC, which may result in changes in motivational approach behavior toward emotionally salient stimuli.

In a recent study, cognitive control (d-prime) on this emotional go/nogo task was examined across a large developmental sample as a function of age and connectivity connectivity between the amygdala and ventral striatum (amygdala-VS) and the amygdala and PFC (Heller et al., 2016). Age predicted improvements in *d'* (Figure 5.1A), and a decrease in amygdala-VS connectivity toward emotional cues. Increased amygdala-VS connectivity also predicted cognitive control to emotional cues, controlling for effects of age (Figure 5.1B). A whole brain analysis relating connectivity with the amygdala to *d'* revealed that *d'* predicted increased connectivity between amygdala and a region of mPFC (Figure 5.2). Furthermore, this mPFC-amygdala connectivity mediated the relationship between amygdala-VS connectivity and *d'* specifically toward emotional cues.

This study reveals that variability in age, subcortical connectivity and cortico-subcortical connectivity interact in producing behavioral output. Furthermore, the degree of connectivity observed changes with age, but also explains variance in the behavior toward emotional stimuli even when controlling for age effects. These findings support a network account of self-control as depending on an interacting circuit of PFC, the amygdala and the ventral striatum, rather than one structure independently, the connections of which change in strength over the course of development (Casey, 2015).

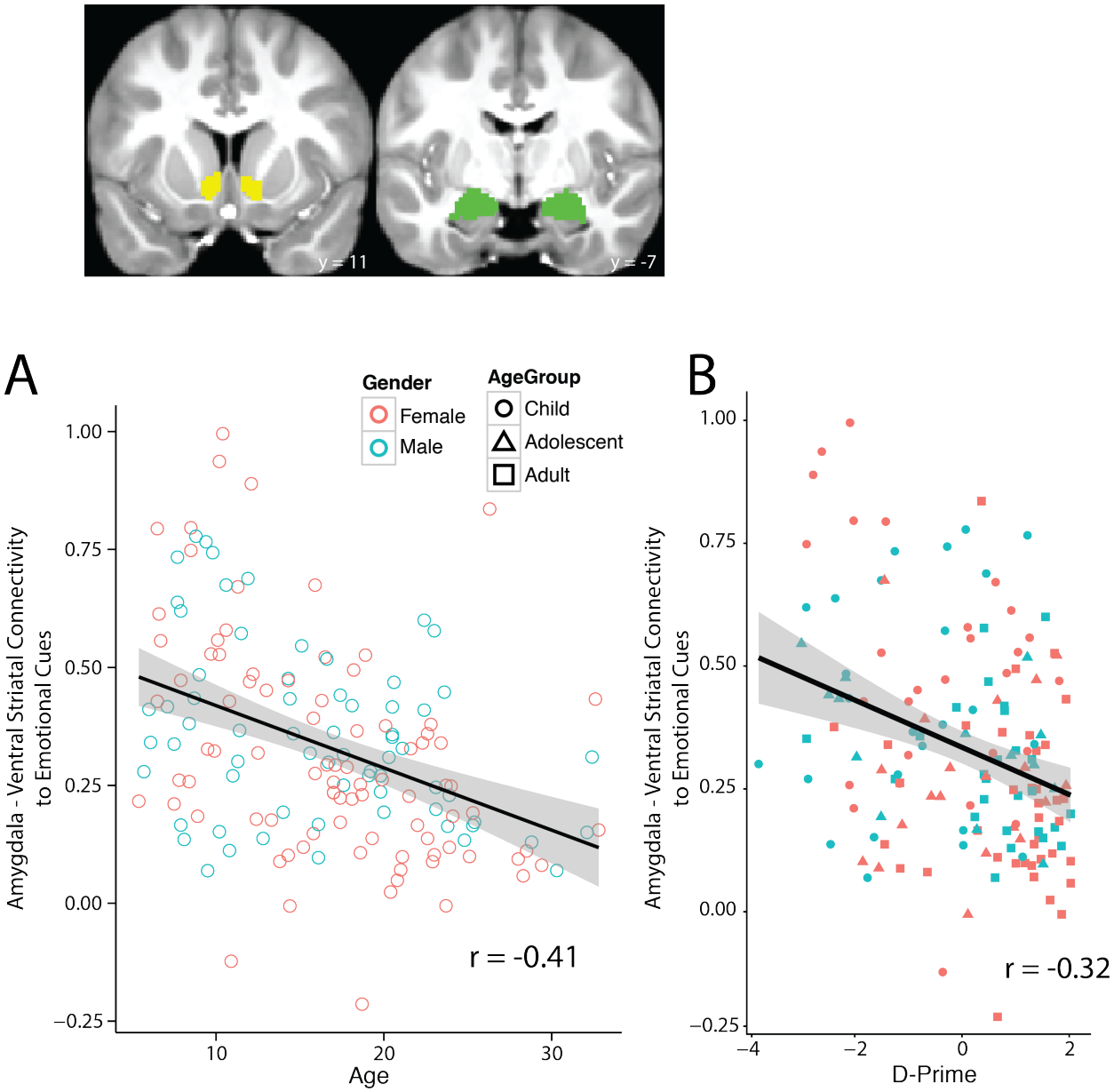

Figure 5.1. Relationships between ventral striatal connectivity and age and d-prime to emotional cues. A) Age predicts decoupling of amygdala ventral-striatal activity. B) Functional connectivity between the amygdala and the ventral striatum related to worse performance.

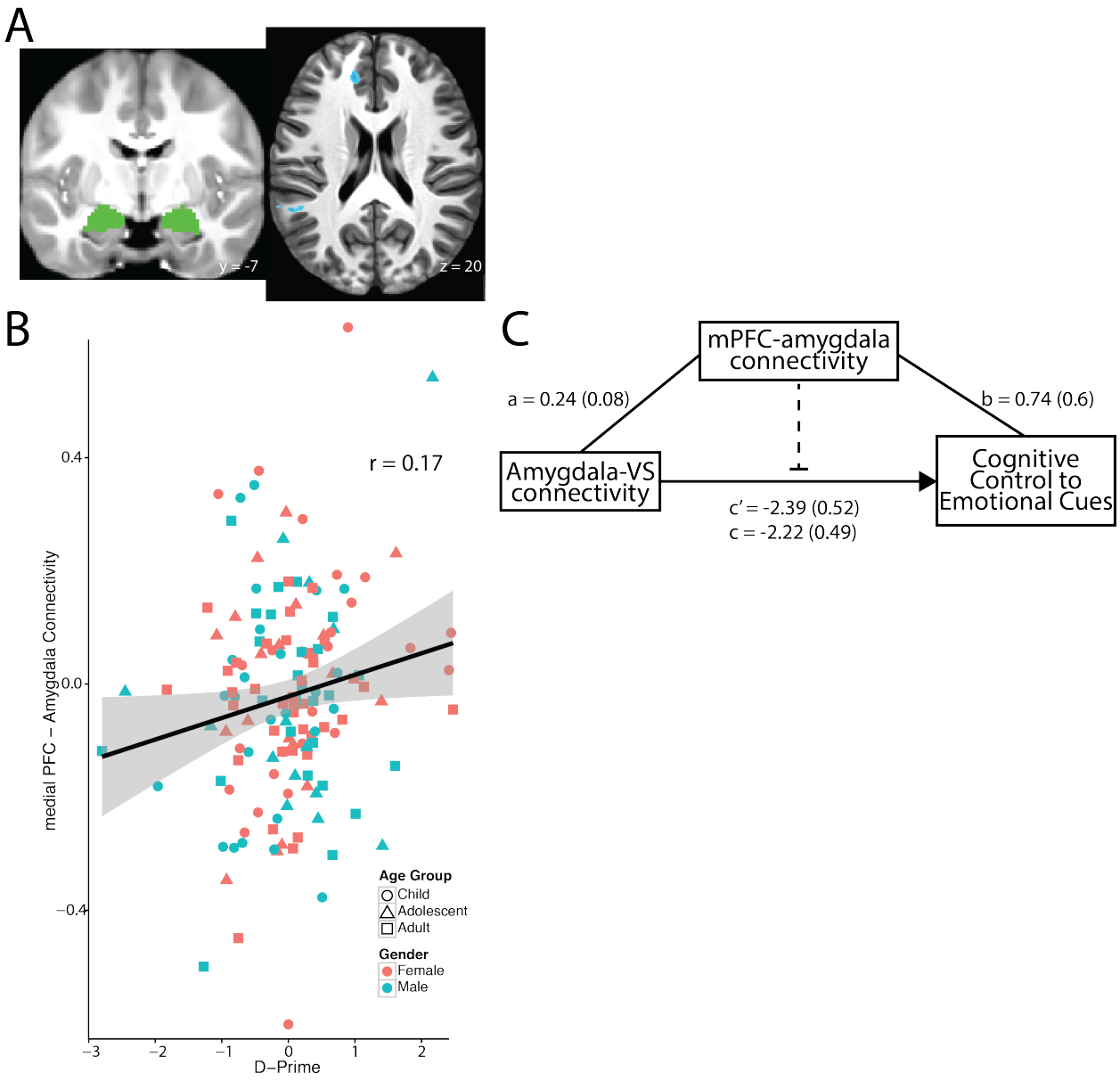

Figure 5.2. Cortico-subcortical connectivity mediates cognitive control toward emotional stimuli. A) The amygdala and medial prefrontal cortex (mPFC) show functional connectivity for emotional (happy and fear cues). B) Functional connectivity between the amygdala and the mPFC related to improved performance. B) amygdala-mPFC connectivity mediated the effect of amygdala-ventral striatum (VS) connectivity on performance.

Individual differences

In Chapter 2, we showed that adolescents showed a particular difficulty in withholding responses to cues of potential threat. While as a group this was true, there was variability between adolescents in their inhibitory control performance toward fear relative to calm faces. Understanding this variability between adolescents may shed light on risk taking behaviors in this age group. High sensation seeking adolescents, for example, have been found to be riskier (Crone, Bullens, van der Plas, Kijkuit, & Zelazo, 2008). Characterizing this variability in impulsivity toward cues of potential threat, could help identify which adolescents are at risk of engaging in criminal activity or developing substance of alcohol abuse.

In Chapters 4 we found that patients with BN were more likely make commission errors toward food cues in particular. Again, between patients with BN other factors may explain greater susceptibility for impulsivity toward appetitive cues. This task could be used with a measure of ad lib eating to examine if this tendency to be drawn to food cues relates to reduced dietary restraint in this patient population.

We also found that individuals with higher anxious eating tendencies were particularly susceptible to make impulse control failures toward food cues under negative emotions. It would be valuable to know if these individual differences can improve with training. Inhibitory practiced has been shown to result in less ad lib consumption immediately after training (Houben & Jansen, 2011). If these tendencies for emotional eating can be changed through training, either temporarily or permanently, would be an interesting future area of study.

Sex differences

Males and females differ in the frequency with which they develop certain psychopathologies. Males more frequently develop externalizing disorders, including antisocial personality disorder and substance abuse disorders (Eaton et al., 2012; Kessler et al., 1994), while females show higher rates of internalizing disorders including depression and anxiety disorders (Angold, Costello, & Worthman, 1998; Ge, Lorenz, Conger, Elder, & Simons, 1994; Ronald C. Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Kessler, Avenevoli, & Ries Merikangas, 2001). BN shows a far greater incidence in females than in males, as well (Hudson et al., 2007). Our studies may shed some light on how differences in impulsivity are related to these different outcomes.

In Chapter two, examining sex differences among adolescence related to different tendencies to exhibit inhibitory control failures. Namely, adolescent males showed heightened impulsivity toward fear faces relative to calm, which drove the adolescent specific increase in false alarm rates to these cues of potential threat. ex differences on this task appear to relate to different behavior and brain activity during successful task performance among adolescents. This adolescent peak in impulsivity toward cues of threat were driven by males, while females recruited frontal control circuitry to a greater extent when successfully withholding responses toward these cues (Figure 2.3). These findings suggest that an ineffective recruitment of frontal regions underlies uninhibited approach behavior toward cues of threat in males. The more unrestrained approach behavior toward the cues of threat exhibited by adolescent males on our task may reflect this tendency of males to act on the environment. Future studies could examine this by implementing this task on developing populations and relating performance to future psychiatric outcomes.

It is important to consider these possibilities in light of the fact that the emotional content of the stimuli used in our paradigms was social in and was the participants focus in responding or trying to withhold their response. In a recent study, Cohen-Gilbert et al., measured inhibitory control across a developmental population using a letter go/nogo paradigm with varying emotional content of task-irrelevant backgrounds. Consistent with our findings, teens (13-14 year-olds) made more false alarms on this task when backgrounds were negative in valence, regardless of sex. Among teens aged 15-16 years old, however, only females showed this same diminished inhibitory control to negative emotions (Cohen-Gilbert & Thomas, 2013). The authors suggested that adolescent females may have more difficulty ignoring negative emotional information, which may relate to their higher rates of developing internalizing disorders. Differences in findings between these two studies may be attributed to the emotional content being the focus of the participant versus task-irrelevant, or to how the emotional information was presented: social versus non-social. Whether male and female teens differ in their ability to withhold responses due to the presentation of the emotional content would be valuable to know given different frequencies of psychiatric diagnoses between sexes. Future studies could examine performance by the same group of male and female adolescents on both tasks to test if the sex differences observed are in fact due to the nature of the emotional content presented. Additionally, as adolescents are particularly susceptible to make risky choices under peer influence (Gardner & Steinberg, 2005), comparing performance to social and non-social stimuli may help separate how emotional and social information impacts teenagers' proclivity to exhibit impulse control failures, even if it is the feature that the participant is attending to. Lastly, Cohen-Gilbert et al. showed younger and older adolescents exhibited different tendencies to make false alarms. Future studies should build on this to take a

more refined look at specific periods within adolescence during which males and females may show sex specific proclivities to make inhibitory control failures when emotional content is involved. Given the emergence of psychopathologies at different time during adolescence, doing this could additionally be implement on a large cohort to examine the predictive ability of this task in the development of problem behaviors.

Females are far more than males are likely to develop BN (Hudson et al., 2007), but what explains this divergent psychiatric outcome is not clear. Societal factors may be implicated in the greater female predisposition toward this eating disorder. Females experience a greater pressure to be thin and more concern for their body image (Striegel-Moore, Silberstein, & Rodin, 1986). Women may also have a more conflicted relationship with food. Females are more preoccupied with food in general (Pettit, Jacob, Page, & Porras, 2010), and are more often dieting or restrained eaters (Haase, Green, & Murphy, 2011). Women may be more likely to overeat when stressed than men, as well (Zellner, Saito, & Gonzalez, 2007; Zellner et al., 2006). On self-report, however, males more frequently report overeating more, while women report loss of control over their eating behavior more (Striegel-Moore et al., 2009). These differences may underlie a real difference in excessive consumption with versus without control, or may be explained by different tendencies in self-report of controlled behavior. Examining sex differences in brain responses to food cues on fMRI studies have shown different patterns of activation between men and women (Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010; S. Frank et al., 2010; Haase et al., 2011), although results on these studies are inconsistent, which may be attributed to small sample sizes.

Our results from Chapters 3 and 4 would suggest that the majority female healthy and eating disordered participants were not different in how they

responded to the negative emotional influences used or in overall inhibitory control. Given the sex differences found in Chapter 2, this may indicate that impulsivity between healthy individuals and patients with BN is more similar than between healthy females and males. Females may be particularly susceptible for developing BN because of their tendency to engage in internalizing disorders (Eaton et al., 2012). Given that negative urgency is a predictive factor for binge eating as well as gambling and substance and alcohol abuse (Fischer, Anderson, & Smith, 2004; Fischer & Smith, 2008), males and females may differ in the psychopathologies they develop based on what they expect to relieve their negative emotions. Indeed, males who have BN symptoms do share commonalities with female patients. Among eating disordered men, poor emotion regulation strategies do relate to body dissatisfaction and disordered eating (Lavender et al., 2015), as in females (Sim and Zeman, 2004; Whiteside et al., 2007). Males and females both show an association between eating to manage negative affect and disordered eating, but difficulties in emotion regulation predict disordered eating in females but not males (Hayaki and Free, 2016). Males who have difficulty in emotional regulation may therefore be less likely to develop binge eating as a maladaptive coping mechanism, perhaps due to a reduced preoccupation with weight and body image, and less conflicted relationship with food.

Individual susceptibilities to develop pathological eating behaviors

Individuals with certain eating tendencies, including restrained and emotional eating are especially susceptible to exhibit dietary failures (Fedoroff et al., 1997; Heatherton et al., 1991), especially when they are experiencing negative emotions (Cools et al., 1992; Oliver et al., 2000; Wardle, Steptoe, Oliver, & Lipsey, 2000). In Chapter 4, we examined the tendency to eat under

anxiety predicted self-control control toward appetitive stimuli when experiencing negative emotions. Individual differences in anxious eating were found to relate to a diminished ability to exhibit successful inhibitory control under a negative emotional state. Future studies could further examine how negative emotions influence brain circuitry involved in motivated behavior toward food. Negative emotional induction have been shown to sensitize reward circuitry for food cues among dieters (D. D. Wagner et al., 2012). Examining the role of negative emotions in dieting and non-dieting populations could show differences as well. Non-dieters may not show an increased sensitivity to food cues under negative emotions, as they're non-dieting status may be due to the fact that they are not susceptible to overeat during negative emotional states. Interestingly, the study by Wagner, et al., used the Velten procedure (Velten, 1968), which involves saying negative statements about oneself to induce negative emotions. Such a procedure may be valuable in studying negative affect in BN, given the relationship between BN and negative self-image (Cooley & Toray, 2001). This kind of negative affect induction may be pertinent to the kind of negative emotions that drive BN psychopathology.

Negative eating expectancy, the expectation that food will relieve negative emotions, is highly associated with BN symptoms (Atlas, 2004; Hayaki, 2009; Hohlstein et al., 1998; G. T. Smith, Simmons, Flory, Annus, & Hill, 2007), especially among women who report high negative urgency (Fischer et al., 2004; Fischer, Settles, et al., 2012). Given differences in their relationship with food, males may more typically turn to substance and alcohol abuse when they perceive these activities as providing relief from negative emotions (Fischer et al., 2004; Fischer, Settles, et al., 2012). Examining how negative urgency and eating expectancies may relate to momentary self-control failures such as on

cognitive tasks like FEAST may reveal more about the process of behavioral disinhibition that results in impulsive behaviors like binge eating.

Implications for treatment of bulimic symptoms

Treatment for BN has typically focused on behavioral modification and medication. Both Cognitive behavioral therapy (CBT) and antidepressants, especially SSRIs, have both shown efficacy in reducing BN symptoms (Hay, 2013; Hay & Claudino, 2010; Mitchell, Agras, & Wonderlich, 2007; Shapiro et al., 2007). Despite these interventions, however, many patients relapse (Grilo et al., 2007; Pamela K. Keel, Dorer, Franko, Jackson, & Herzog, 2005), and 30-50% of patients are symptomatic ten years after initial treatment (Hay & Claudino, 2010; Keel, Mitchell, Miller, Davis, & Crow, 2000), leaving much room for improvement in treating this disorder.

In Chapter 3, we observed that sustained states of positive affect predicted improved cognitive performance among patients with BN. These findings suggest that addressing emotional aspects could relate to improved performance. Recently, novel treatments for BN have focused on changing the relationship between emotions and behaviors. Integrative cognitive-affective therapy (ICAT) is aimed at modifying emotional experiences as they are linked to action tendencies (Wonderlich et al., 2008). ICAT may be as effective as CBT at reducing BN symptoms (Wonderlich et al., 2014), although no studies have examined long-term outcomes rates to examine maintenance of remission. The effectiveness of this treatment may lie in addressing the expectancy that food will relieve negative emotions, which have been shown to predict remission rates (Bohon, Stice, & Burton, 2009; Pearson et al., 2015). While this new tool is a step forward in improving treatment for BN symptoms, findings from our study may

suggest that future treatments may benefit from enhancing and maintaining positive affect as well.

Positive emotions may mitigate binge eating behaviors in two ways. First, positive affect has been shown to relate to greater experience of pleasantness while eating (M Macht, 1999; Michael Macht, 2008). The gustatory and reward systems of patients with BN may be hypofunctioning in response to receipt of food (Bohon & Stice, 2011), which may drive overeating as a compensatory mechanism. If that is the case, maintaining positive affect may help increase appreciation of food, promoting eating for enjoyment and satiety rather than for compulsion. Additionally, positive emotional states have been found to improve cognitive control and performance among healthy individuals (Ashby, Valentin, & Turken, 2002; Cohen, Dellarco, et al., 2016; Fredrickson & Branigan, 2005). In BN, as well, maintaining positive affect in addition to reducing negative affect may provide improved control over eating behavior.

It is important to consider this proposition about positive affect in the context of a discrepancy between findings on in Chapters 3 and 4. Patient behavior was not affected by the positive emotional manipulation on the FEAST. A potential explanation for this difference in effect is that food cues may be more salient to patients with BN than the social emotional cues used in the CCUE. Patients may therefore not be responding to the emotional manipulation of FEAST because their focus is more directed to the cues, resulting in a relatively diminished effect of the emotional states on behavior. These tasks are also different in two important ways that may impact performance. First, the CCUE task uses a jittered inter-trial interval (ITI) for the purpose of separating BOLD signal between trial types on fMRI analysis, while the ITI was constant on FEAST. The longer ITI difference may have given patients more time between trials to focus on their emotional state, giving the emotional state more influence

over their behavior. The regular rate of occurrence of cues during FEAST, in contrast, means that the presentation of cues is more predictable, making it easier to focus on cues over emotional states. Additionally, patients were seated at a computer terminal during performance of FEAST, but were supine in the MRI scanner for the CCUE task. These different environmental conditions may have impacted task performance between the two tasks in ways that are difficult to account for. Finally, the difference in behavior on these tasks may indicate non-replication of the positive emotional finding. Future studies would need to replicate this finding to verify and further explore the role of positive affect on enhancing cognitive control among patients with BN. A better understanding of how positive emotions may contribute to improved cognitive control among patients, and what neural circuitry is implicated in that performance could open new avenues for treatments for BN symptoms.

Bulimia nervosa is a heterogeneous disease that shares high rates of comorbidity with other psychiatric conditions (Blinder, Cumella, & Sanathara, 2006; Godart et al., 2007). Understanding treatment response and improving outcomes will also require taking a more refined approach in examining which factors are predictive of symptom reduction and sustained long-term remission. Individual differences between patients with has shown predictive power for remission rates (Bohon, Stice, & Burton, 2009). Better characterizing the heterogeneity of condition will help understand what drives symptoms in a given individual, and may further improve treatments and remission rates. Furthermore, it would open the door to examining how to categorize which patients are responsive to which treatments, which could lead to more personalized application of existing treatments and the delopment of improved treatment stategies for subcategories of patients with BN who experience less benefit from existing treatment modalities.

General limitations

General limitations of the methodology used should be critically considered in interpreting the results presented in this thesis. Behavioral analyses of the go/nogo paradigms implemented in these studies typically focused on two measures. Failures to withhold inappropriate responses to nogo trials were examined as representing susceptibility to inhibitory control failure, while *d'*, a composite measure including performance to go and nogo trials, was interpreted to indicate successful cognitive control across changing task demands. These interpretations, while certainly reasonable, have limitations. False alarm rate measures inappropriate responses, but without relation to a baseline of appropriate responses. Dissociating whether observed differences in false alarm rate are due to increased motivational drive or impaired inhibitory control is therefore not possible with this measure alone. Additionally, D-prime, as a sort of composite accuracy score, is not sensitive to pervasive changes in approach behavior when they occur. If a condition or group predicts overall comparably enhanced approach behavior on both go and nogo trials, for example, *d'* will change as hit and false alarm rates will both increase. Although this may be valid in reflecting no overall change in task performance or accuracy, examining behavior by overall approach behavior may reveal differences in behavior related to motivation or arousal. Overall, these limitations in behavioral conclusions support the use of multiple analysis techniques, and comparable measures of task performance from other paradigms such as flanker, Stroop and stop signal tasks to further investigate what drives differences in behavior.

Regarding fMRI analysis, we have taken the approach of relating neural activation on successful trials to task performance. While this approach does constrain our interpretation of the imaging data, it depends on the inference that recruitment during successful response inhibitions may underlie individual or

group differences in behavior. Additional analysis may look at activation on successful vs unsuccessful nogo trials, although a limitation of the task paradigm is that some participants exhibit near ceiling performance and do not have sufficient incorrect trials to model unsuccessful trials. This relationship between task performance and neural activation is especially drawn into question when BOLD signal does not predict or relate to behavior. Understanding why regions, networks or connectivity changes in parallel to behavior but does not predict it is an interesting question to address in future studies.

It is important to consider ~~out~~ findings on BN in light of the fact that we did not have control diagnostic groups. Bulimia nervosa is highly comorbid with other diagnoses (Hudson et al., 2007). Additionally, the many of the core features of BN including loss of control over eating behavior are not unique to this diagnosis. Therefore, before we can specifically attribute differences in performance or neural activity to this diagnosis, rather than a general effect of being a psychiatric patient, or being driven by a trait that is shared between across patient groups such as negative urgency. Studies comparing diagnostic groups, for example, have shown that high negative urgency is common to BN and alcohol and substance abuse, but the specific combination of negative urgency and negative eating expectancy differentiates BN (Pearson et al., 2015). Studies will require comparison groups with other psychiatric conditions to better isolate what may be unique to BN. These kinds of studies would further allow for a better understanding of what specifically predisposes individuals to develop BN, and open the door for more directed identification of at-risk children and teens, and the emergence of more effective treatments and preventions.

Lastly, all the studies presented here involve small sample sizes. While the results observed are consistent with the literature they warrant replication. In small sample sized in particular, idiosyncratic differences may exist between

groups that could contribute to or account for behavioral and neuroimaging effects observed.

Conclusions

Self-control behavior varies between individuals and circumstances. Understanding this variability and how it changes over development can lead to a better understanding of what situations and cues result in the breakdown of self-control, and of pathologies involving lapses in self-control like BN. In this thesis, we demonstrated that self-control is diminished during adolescence toward emotional cues of potential threat in particular. We further showed that patients with BN fail to show the typical improvements with age in cognitive control which is paralleled by diminished recruitment of prefrontal regions relative to healthy participants. This neural and behavioral finding may relate to the onset or maintenance of BN in this group. We found enhanced cognitive control under positive emotions for patients with BN, which we suggest may have implications for a role of positive emotions in symptom management. Patients with BN further exhibited a particularly high rate of impulse control failures toward food cues, while HCs showed diminished impulse control to food cues under negative emotions. We suggest that our findings reveal a deeper understanding of the individual and situations that underlie self-control failures, and may provide valuable next steps in examining treatments for individuals with a tendency to exhibit self-control.

REFERENCES

Abraham, S. F., & Beumont, P. J. (1982). How patients describe bulimia or binge eating. *Psychological Medicine*, *12*(3), 625–35. http://doi.org/10.1017/S0033291700055732

Adam, T. C., & Epel, E. S. (2007). Stress, eating and the reward system. *Physiology & Behavior*, *91*(4), 449–58. http://doi.org/10.1016/j.physbeh.2007.04.011

Adleman, N. E., Menon, V., Blasey, C. M., White, C. D., Warsofsky, I. S., Glover, G. H., & Reiss, A. L. (2002). A developmental fMRI study of the Stroop color-word task. *Neuroimage*, *16*(1), 61–75. http://doi.org/10.1006/nimg.2001.1046

Alpers, G. W., & Tuschen-Caffier, B. (2001). Negative feelings and the desire to eat in bulimia nervosa. *Eating Behaviors*, *2*(4), 339–352. http://doi.org/10.1016/S1471-0153(01)00040-X

American Psychiatric Association. (2013). *DSM 5*. *American Journal of Psychiatry*. http://doi.org/10.1176/appi.books.9780890425596.744053

Anestis, M. D., Smith, A. R., Fink, E. L., & Joiner, T. E. (2009). Dysregulated eating and distress: Examining the specific role of negative urgency in a clinical sample. *Cognitive Therapy and Research*, *33*(4), 390–397. http://doi.org/10.1007/s10608-008-9201-2

Angold, A., Costello, E. J., & Worthman, C. M. (1998). Puberty and depression: The roles of age, pubertal status and pubertal timing. *Psychological Medicine*, *28*(1), 51–61. http://doi.org/10.1017/S003329179700593X

Arnett, J. (1992). Reckless behavior in adolescence: A developmental perspective. *Developmental Review*, *12*(4), 339–373. http://doi.org/10.1016/0273-2297(92)90013-R

Arnett, J. J. (1999). Adolescent storm and stress, reconsidered. *The American Psychologist*, *54*(5), 317–26. http://doi.org/10.1037/0003-066X.54.5.317

Arnow, B., Kenardy, J., & Agras, W. S. (1995). The Emotional Eating Scale: the development of a measure to assess coping with negative affect by eating. *The International Journal of Eating Disorders*, *18*, 79–90. http://doi.org/10.1002/1098-108X(199507)18:1<79::AID-EAT2260180109>3.0.CO;2-V

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews. Neuroscience*, *10*(6), 410–22. http://doi.org/10.1038/nrn2648

Aron, A. R., Robbins, T. W., & Poldrack, R. a. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, *8*(4), 170–177. http://doi.org/10.1016/j.tics.2004.02.010

Aron, A. R., Robbins, T. W., & Poldrack, R. a. (2014). Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*, *18*(4), 177–185. http://doi.org/10.1016/j.tics.2013.12.003

Asato, M. R., Terwilliger, R., Woo, J., & Luna, B. (2010). White matter

development in adolescence: A DTI study. *Cerebral Cortex*, *20*(9), 2122–2131. http://doi.org/10.1093/cercor/bhp282

Ashby, G., Valentin, V., & Turken, U. (2002). The effects of positive affect and arousal on working memory and executive attention: Neurobiology and computational models. *Emotional Cognition: From Brain to Behaviour*, 245–287. Retrieved from https://books.google.com/books?hl=en&lr=&id=YI-GK7k2hI4C&oi=fnd&pg=PA245&dq=The+effects+of+positive+affect+and+arousal+on+working+memory+and+executive+attention:+neurobiology+and+com-+putational+models&ots=L-sgZ62RGb&sig=dE26FnrvKyDZqhfNnpuYWQTtAYc

Atlas, J. G. (2004). Interpersonal sensitivity, eating disorder symptoms, and eating/ thinness expectancies. *Current Psychology*, *22*(4), 368–378. http://doi.org/10.1007/s12144-004-1041-y

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Luan Phan, K. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*(4), 303–312. http://doi.org/10.1093/scan/nsm029

Bates, D., Maechler, M., Bolker, B., & Walker, S. (2014). lme4: linear mixed-effects models using S4 classes. R package version 1.1-6. *R*. Retrieved from http://cran.r-project.org/package=lme4

Beaver, J. D., Lawrence, A. D., van Ditzhuijzen, J., Davis, M. H., Woods, A., & Calder, A. J. (2006). Individual differences in reward drive predict neural responses to images of food. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(19), 5160–6. http://doi.org/10.1523/JNEUROSCI.0350-06.2006

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*, *123*, 2189–2202. http://doi.org/10.1093/brain/123.11.2189

Berg, K. C., Crosby, R. D., Cao, L., Peterson, C. B., Engel, S. G., Mitchell, J. E., & Wonderlich, S. A. (2013). Facets of negative affect prior to and following binge-only, purge-only, and binge/purge events in women with bulimia nervosa. *Journal of Abnormal Psychology*, *122*(1), 111–8. http://doi.org/10.1037/a0029703

Berner, L. a., & Marsh, R. (2014). Frontostriatal Circuits and the Development of Bulimia Nervosa. *Frontiers in Behavioral Neuroscience*, *8*(November), 1–12. http://doi.org/10.3389/fnbeh.2014.00395

Berridge, K. C. (1996). Food Reward : Brain Substrates of Wanting and Liking. *Neuroscience and Biobehavioral Reviews*, *20*(1), 1–25. http://doi.org/10.1016/0149-7634(95)00033-B

Berridge, K. C. (2009). “Liking” and “wanting” food rewards: Brain substrates and roles in eating disorders. *Physiology and Behavior*, *97*(5), 537–550. http://doi.org/10.1016/j.physbeh.2009.02.044

Best, J., & Miller, P. (2010). A Developmental Perspective on Executive Function. *Child Development*, *81*(6), 1641–1660. http://doi.org/10.1111/j.1467-

8624.2010.01499.x.A

Blakemore, S.-J. (2008). The social brain in adolescence. *Nat Rev Neurosci*, *9*(4), 267–277. JOUR. Retrieved from http://dx.doi.org/10.1038/nrn2353

Blinder, B. J., Cumella, E. J., & Sanathara, V. a. (2006). Psychiatric comorbidities of female inpatients with eating disorders. *Psychosomatic Medicine*, *68*(3), 454–62. http://doi.org/10.1097/01.psy.0000221254.77675.f5

Boeka, A. G., & Lokken, K. L. (2006). The Iowa gambling task as a measure of decision making in women with bulimia nervosa. *Journal of the International Neuropsychological Society : JINS*, *12*(5), 741–745. http://doi.org/10.1017/S1355617706060887

Bohon, C., & Stice, E. (2011). Reward abnormalities among women with full and subthreshold bulimia nervosa: a functional magnetic resonance imaging study. *The International Journal of Eating Disorders*, *44*(7), 585–95. http://doi.org/10.1002/eat.20869

Bohon, C., & Stice, E. (2012). Negative affect and neural response to palatable food intake in bulimia nervosa. *Appetite*, *58*(3), 964–970. http://doi.org/10.1016/j.appet.2012.02.051

Bohon, C., Stice, E., & Burton, E. (2009). Maintenance factors for persistence of bulimic pathology: A prospective natural history study. *International Journal of Eating Disorders*, *42*(2), 173–178. http://doi.org/10.1002/eat.20600

Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature*, *402*(6758), 179–181. http://doi.org/10.1038/46035

Bourgeois, J., & Goldman-rakic, P. S. (1994). Synaptogenesis in the Prefrontal Cortex of Rhesus Monkeys.

Bourgeois, J. P., Jastreboff, P. J., & Rakic, P. (1989). Synaptogenesis in visual cortex of normal and preterm monkeys: evidence for intrinsic regulation of synaptic overproduction. *Proceedings of the National Academy of Sciences of the United States of America*, *86*(11), 4297–301. http://doi.org/10.1073/pnas.86.11.4297

Bouwmeester, H., Smits, K., & Van Ree, J. M. (2002). Neonatal development of projections to the basolateral amygdala from prefrontal and thalamic structures in rat. *Journal of Comparative Neurology*, *450*(3), 241–255. http://doi.org/10.1002/cne.10321

Breiter, H. C., Aharon, I., Kahneman, D., Dale, A., & Shizgal, P. (2001). Functional Imaging of Neural Resposes to Monetary Gains and Losses. *Neuron*, *30*(May), 619–639. http://doi.org/10.1016/S0896-6273(01)00303-8

Breiter, H. C., Gollub, R. L., Weisskoff, R. M., Kennedy, D. N., Makris, N., Berke, J. D., … Hyman, S. E. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron*, *19*(3), 591–611. http://doi.org/10.1016/S0896-6273(00)80374-8

Brockmeyer, T., Skunde, M., Wu, M., Bresslein, E., Rudofsky, G., Herzog, W., & Friederich, H.-C. (2014). Difficulties in emotion regulation across the

spectrum of eating disorders. *Comprehensive Psychiatry*, *55*(3), 565–71. http://doi.org/10.1016/j.comppsych.2013.12.001

Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Jou, J., Tiongson, E., Allen, V., … Cohen, M. S. (2007). Neural Substrates of Resisting Craving During Cigarette Cue Exposure. *Biological Psychiatry*, *62*(6), 642–651. http://doi.org/10.1016/j.biopsych.2006.10.026

Brooks, S. J., O'Daly, O. G., Uher, R., Friederich, H.-C., Giampietro, V., Brammer, M., … Campbell, I. C. (2011). Differential neural responses to food images in women with bulimia versus anorexia nervosa. *PloS One*, *6*(7), e22259. http://doi.org/10.1371/journal.pone.0022259

Brooks, S., Prince, A., Stahl, D., Campbell, I. C., & Treasure, J. (2011). A systematic review and meta-analysis of cognitive bias to food stimuli in people with disordered eating behaviour. *Clinical Psychology Review*, *31*(1), 37–51. http://doi.org/10.1016/j.cpr.2010.09.006

Brown, T. T., Lugar, H. M., Coalson, R. S., Miezin, F. M., Petersen, S. E., & Schlaggar, B. L. (2005). Developmental changes in human cerebral functional organization for word generation. *Cerebral Cortex*, *15*(3), 275–290. http://doi.org/10.1093/cercor/bhh129

Buhle, J. T., Silvers, J. A., Wage, T. D., Lopez, R., Onyemekwu, C., Kober, H., … Ochsner, K. N. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex*, *24*(11), 2981–2990. http://doi.org/10.1093/cercor/bht154

Call, K. T., Reidel, A. A., Hein, K., McLoyd, V., Petersen, A., & Kipke, M. (2002). Adolescent health and well-being in the twenty-first century: A global perspective. *Journal of Research on Adolescence*, *12*(1), 69–98.

Casey, B. J. (2015). Beyond Simple Models of Self-Control to Circuit-Based Accounts of Adolescent Behavior. *Annual Review of Psychology*, *66*, 295–319. http://doi.org/10.1146/annurev-psych-010814-015156

Casey, B. J., & Caudle, K. (2013). The Teenage Brain: Self Control. *Current Directions in Psychological Science*, *22*(2), 82–87. http://doi.org/10.1177/0963721413480170

Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology*, *54*(1–3), 241–257. http://doi.org/10.1016/S0301-0511(00)00058-2

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*, *1124*, 111–126. http://doi.org/10.1196/annals.1440.010

Casey, B. J., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biological Psychiatry*, *76*(5), 350–353. http://doi.org/10.1016/j.biopsych.2014.01.006

Casey, B. J., Somerville, L. H., Gotlib, I. H., Ayduk, O., Franklin, N. T., Askren, M. K., … Shoda, Y. (2011). Behavioral and neural correlates of delay of gratification 40 years later. *Proceedings of the National Academy of*

Sciences of the United States of America, *108*(36), 14998–5003. http://doi.org/10.1073/pnas.1108561108

Casey, B. J., Thomas, K. M., Welsh, T. F., Badgaiyan, R. D., Eccard, C. H., Jennings, J. R., & Crone, E. a. (2000). Dissociation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences*, *97*(15), 8728–33. http://doi.org/10.1073/pnas.97.15.8728

Cauffman, E., Shulman, E. P., Steinberg, L., Claus, E., Banich, M. T., Graham, S., & Woolard, J. (2010). Age differences in affective decision making as indexed by performance on the Iowa Gambling Task. *Developmental Psychology*, *46*(1), 193–207. http://doi.org/10.1037/a0016128

Chambers, R. A., & Potenza, M. N. (2003). Neurodevelopment, impulsivity, and adolescent gambling. *Journal of Gambling Studies*, *19*(1), 53–84. http://doi.org/10.1023/A:1021275130071

Chambers, R. A., Taylor, J. R., & Potenza, M. N. (2003). Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *American Journal of Psychiatry*, *160*(6), 1041–1052. http://doi.org/10.1176/appi.ajp.160.6.1041

Chassin, L., Hussong, A., Barrera, M., Molina, B., Trim, R., & Ritter, J. (2004). Adolescent substance use. In *Handbook of adolescent psychology*.

Chassin, L., Presson, C. C., Rose, J. S., & Sherman, S. J. (1996). The Natural History of Cigarette Smoking From Adolescence to Adulthood: Demographic Predictors of Continuity and Change. *Health Psychology*, *15*(6), 478–484. http://doi.org/10.1037/0278-6133.15.6.478

Chechik, G., Meilijson, I., & Ruppin, E. (1998). Synaptic Pruning in Development: A Computational Account. *Neural Computation*, *10*(7), 1759–1777. http://doi.org/10.1162/089976698300017124

Chechik, G., Meilijson, I., & Ruppin, E. (1999). Neuronal regulation: A mechanism for synaptic pruning during brain maturation. *Neural Computation*, *11*(8), 2061–80. http://doi.org/10.1162/089976699300016089

Chein, J. M., Albert, D., O'Brien, L., Uckert, K., & Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Developmental Science*, *14*(2), 1–10. http://doi.org/10.1111/j.1467-7687.2010.01035.x

Chen, G., Saad, Z. S., Britton, J. C., Pine, D. S., & Cox, R. W. (2013). Linear mixed-effects modeling approach to FMRI group analysis. *NeuroImage*, *73*, 176–190. http://doi.org/10.1016/j.neuroimage.2013.01.047

Chen, G., Saad, Z. S., Nath, A. R., Beauchamp, M. S., & Cox, R. W. (2012). FMRI group analysis combining effect estimates and their variances. *NeuroImage*, *60*(1), 747–765. http://doi.org/10.1016/j.neuroimage.2011.12.060

Chen, K., & Kandel, D. B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. *American Journal of Public Health*, *85*(1), 41–47. http://doi.org/10.2105/AJPH.85.1.41

Chugani, H. T., Phelps, M. E., & Mazziotta, J. C. (1987). Positron emission tomography study of human brain functional development. *Annals of Neurology*, *22*(4), 487–497. http://doi.org/10.1002/ana.410220408

Claes, L., Vandereycken, W., & Vertommen, H. (2005). Impulsivity-related traits in eating disorder patients. *Personality and Individual Differences*, *39*(4), 739–749. http://doi.org/10.1016/j.paid.2005.02.022

Cohen-Gilbert, J. E., & Thomas, K. M. (2013). Inhibitory control during emotional distraction across adolescence and early adulthood. *Child Development*, *84*(6), 1954–1966. http://doi.org/10.1111/cdev.12085

Cohen, A. O., Breiner, K., Steinberg, L., Bonnie, R. J., Scott, E. S., Taylor-Thompson, K. A., … Casey, B. J. (2016). When Is an Adolescent an Adult? Assessing Cognitive Control in Emotional and Nonemotional Contexts. *Psychological Science*. http://doi.org/10.1177/0956797615627625

Cohen, A. O., Dellarco, D. V, Breiner, K., Helion, C., Heller, A. S., Rahdar, A., … Casey, B. J. (2016). The Impact of Emotional States on Cognitive Control Circuitry and Function. *Journal of Cognitive Neuroscience*, *28*(3), 446–459. http://doi.org/10.1162/jocn_a_00906

Cooley, E., & Toray, T. (2001). Body image and personality predictors of eating disorder symptoms during the college years. *International Journal of Eating Disorders*, *30*(1), 28–36. http://doi.org/10.1002/eat.1051

Cools, J., Schotte, D. E., & McNally, R. J. (1992). Emotional arousal and overeating in restrained eaters. *Journal of Abnormal Psychology*, *101*(2), 348–351. http://doi.org/10.1037/0021-843X.101.2.348

Cornier, M. A., Salzberg, A. K., Endly, D. C., Bessesen, D. H., & Tregellas, J. R. (2010). Sex-based differences in the behavioral and neuronal responses to food. *Physiology and Behavior*, *99*(4), 538–543. http://doi.org/10.1016/j.physbeh.2010.01.008

Covington, H. E., & Miczek, K. A. (2005). Intense cocaine self-administration after episodic social defeat stress, but not after aggressive behavior: Dissociation from corticosterone activation. *Psychopharmacology*, *183*(3), 331–340. http://doi.org/10.1007/s00213-005-0190-5

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal*, *29*, 162–173. http://doi.org/10.1006/cbmr.1996.0014

Crone, E. A., Bullens, L., van der Plas, E. A. A., Kijkuit, E. J., & Zelazo, P. D. (2008). Developmental changes and individual differences in risk and perspective taking in adolescence. *Development and Psychopathology*, *20*(4), 1213–29. http://doi.org/10.1017/S0954579408000588

Crosby, R. D., Wonderlich, S. a., Engel, S. G., Simonich, H., Smyth, J., & Mitchell, J. E. (2009). Daily mood patterns and bulimic behaviors in the natural environment. *Behaviour Research and Therapy*, *47*(3), 181–188. http://doi.org/10.1016/j.brat.2008.11.006

Crow, S. J., Peterson, C. B., Swanson, S. A., Raymond, N. C., Specker, S., Eckert, E. D., & Mitchell, J. E. (2009). Increased mortality in bulimia nervosa

and other eating disorders. *The American Journal of Psychiatry*, *166*, 1342–1346. http://doi.org/10.1176/appi.ajp.2009.09020247

D'Unger, A. V, Land, K. C., & McCall, P. L. (2002). Sex Differences in Age Patterns of Delinquent/Criminal Careers: Results from Poisson Latent Class Analyses of the Philadelphia Cohort Study. *Journal of Quantitative Criminology*, *18*(4), 349–375. JOUR. http://doi.org/10.1023/A:1021117626767

Davidson, M. C., Amso, D., Anderson, L. C., & Diamond, A. (2006). Development of cognitive control and executive functions from 4 to 13 years: Evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia*, *44*(11), 2037–2078. http://doi.org/10.1016/j.neuropsychologia.2006.02.006

Davis, F. C., Somerville, L. H., Ruberry, E. J., Berry, A. B. L., Shin, L. M., & Whalen, P. J. (2011). A tale of two negatives: differential memory modulation by threat-related facial expressions. *Emotion (Washington, D.C.)*, *11*(3), 647–655. http://doi.org/10.1037/a0021625

Davis, R. J., Garner, D. M., & Freeman, R. (1988). A naturalistic investigation of eating behavior in bulimia nervosa. *Journal of Consulting and Clinical Psychology\n*, *56*(2), 273–279. http://doi.org/10.1037/0022-006X.56.2.273

Dawe, S., & Loxton, N. J. (2004). The role of impulsivity in the development of substance use and eating disorders. *Neuroscience and Biobehavioral Reviews*, *28*(3), 343–351. http://doi.org/10.1016/j.neubiorev.2004.03.007

Delgado, M. R., Nystrom, L. E., Fissell, C., Noll, D. C., & Fiez, J. a. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*, *84*(6), 3072–3077. http://doi.org/10.1016/0166-2236(90)90107-l

DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M., & Tataranni, P. A. (2007). Successful dieters have increased neural activity in cortical areas involved in the control of behavior. *International Journal of Obesity*, *31*(3), 440–448. http://doi.org/10.1038/sj.ijo.0803431

Demos, K., Kelley, W. M., & Heatherton, T. F. (2011). Dietary restraint violations influence reward responses in nucleus accumbens and amygdala. *Journal of Cognitive Neuroscience*, *23*(8), 1952–1963. http://doi.org/10.1162/jocn.2010.21568.Dietary

Deroche, V., Marinelli, M., Maccari, S., Le Moal, M., Simon, H., & Piazza, P. V. (1995). Stress-induced sensitization and glucocorticoids. I. Sensitization of dopamine-dependent locomotor effects of amphetamine and morphine depends on stress-induced corticosterone secretion. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *15*(11), 7181–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7472472

Desikan, R. S., S??gonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. http://doi.org/10.1016/j.neuroimage.2006.01.021

Di Chiara, G., Bassareo, V., Fenu, S., De Luca, M. A., Spina, L., Cadoni, C., … Lecca, D. (2004). Dopamine and drug addiction: The nucleus accumbens shell connection. *Neuropharmacology*, *47*(SUPPL. 1), 227–241. http://doi.org/10.1016/j.neuropharm.2004.06.032

Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature*. http://doi.org/10.1038/380069a0

Douglas, L. A., Varlinskaya, E. I., & Spear, L. P. (2003). Novel-object place conditioning in adolescent and adult male and female rats: effects of social isolation. *Physiology & Behavior*, *80*(2–3), 317–325. http://doi.org/10.1016/j.physbeh.2003.08.003

Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, A. A., … Mathis, C. A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biological Psychiatry*, *49*(2), 81–96. http://doi.org/10.1016/S0006-3223(00)01038-6

Dreyfuss, M., Caudle, K., Drysdale, A. T., Johnston, N. E., Cohen, A. O., Somerville, L. H., … Casey, B. J. (2014a). Teens Impulsively React rather than Retreat from Threat. *Developmental Neuroscience*, pp. 220–227. http://doi.org/10.1159/000357755

Dreyfuss, M., Caudle, K., Drysdale, A. T., Johnston, N. E., Cohen, A. O., Somerville, L. H., … Casey, B. J. (2014b). Teens Impulsively React rather than Retreat from Threat. *Developmental Neuroscience*, *36*(3–4), 220–227. http://doi.org/10.1159/000357755

Duckworth, A. L., & Seligman, M. E. P. (2012). Outdoes IQ Self-Discipline in Predicting Academic Performance of Adolescents. *Psychological Science*, *16*(12), 939–944.

Durston, S., Davidson, M. C., Tottenham, N., Galvan, A., Spicer, J., Fossella, J. A., & Casey, B. J. (2006). A shift from diffuse to focal cortical activity with development. *Developmental Science*, *9*(1), 1–20. http://doi.org/10.1111/j.1467-7687.2005.00454.x

Durston, S., Thomas, K. M., Yang, Y., Uluğ, A. M., Zimmerman, R. D., & Casey, B. J. (2002). A neural basis for the development of inhibitory control. *Developmental Science*, *5*, 9–16. http://doi.org/10.1111/1467-7687.00235

Eaton, N. R., Keyes, K. M., Krueger, R. F., Balsis, S., Skodol, A. E., Markon, K. E., … Hasin, D. S. (2012). An invariant dimensional liability model of gender differences in mental disorder prevalence: evidence from a national sample. *Journal of Abnormal Psychology*, *121*(1), 282–8. http://doi.org/10.1037/a0024780

Eigsti, I. M., Zayas, V., Mischel, W., Shoda, Y., Ayduk, O., Dadlani, M. B., … Casey, B. J. (2006). Predicting cognitive control from preschool to late adolescence and young adulthood. *Psychological Science*, *17*(6), 478–484. http://doi.org/10.1111/j.1467-9280.2006.01732.x

Enns, J. T., & Cameron, S. (1987). Selective attention in young children: The relations between visual search, filtering, and priming. *Journal of*

Experimental Child Psychology, *44*(1), 38–63. http://doi.org/10.1016/0022-0965(87)90021-X

Epel, E., Lapidus, R., McEwen, B., & Brownell, K. (2001). Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology*, *26*(1), 37–49. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11070333

Ernst, M., Nelson, E. E., Jazbec, S., McClure, E. B., Monk, C. S., Leibenluft, E., … Pine, D. S. (2005). Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *NeuroImage*, *25*(4), 1279–1291. http://doi.org/10.1016/j.neuroimage.2004.12.038

Ernst, M., Pine, D. S., & Hardin, M. (2006). Triadic model of the neurobiology of motivated behavior in adolescence. *Pshychological Medicine*, *36*(September 2005), 299–312. http://doi.org/10.1017/S0033291705005891

Ernst, M., Romeo, R. D., & Andersen, S. L. (2009). Neurobiology of the development of motivated behaviors in adolescence: A window into a neural systems model. *Pharmacology Biochemistry and Behavior*, *93*(3), 199–211. http://doi.org/10.1016/j.pbb.2008.12.013

Fairburn, C. G., Cooper, Z., & Connor, M. O. (2008). Eating Disorder Examination (Edition 16.0D). *Cognitive Behavior Therapy and Eating Disorders*, (1994), 1–49. http://doi.org/10.1037/t03975-000

Fairburn, C. G., & Harrison, P. J. (2003). Eating disorders. In *Lancet* (Vol. 361, pp. 407–416). http://doi.org/10.1016/S0140-6736(03)12378-1

Fareri, D. S., Gabard-Durnam, L., Goff, B., Flannery, J., Gee, D. G., Lumian, D. S., … Tottenham, N. (2015). Normative development of ventral striatal resting state connectivity in humans. *NeuroImage*, *118*, 422–437. http://doi.org/10.1016/j.neuroimage.2015.06.022

Fedoroff, I. C., Polivy, J., & Herman, C. P. (1997). The effect of pre-exposure to food cues on the eating behavior of restrained and unrestrained eaters. *Appetite*, *28*, 33–47. http://doi.org/10.1006/appe.1996.0057

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience*, *13*(5), 538–539. http://doi.org/10.1038/nn.2516

Fioravanti, G., Castellini, G., Lo Sauro, C., Ianni, S., Montanelli, L., Rotella, F., … Ricca, V. (2014). Course and moderators of emotional eating in anorectic and bulimic patients: A follow-up study. *Eating Behaviors*, *15*(2), 192–196. http://doi.org/10.1016/j.eatbeh.2014.01.006

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. for DSMIV*.

Fischer, S., Anderson, K. G., & Smith, G. T. (2004). Coping with distress by eating or drinking: role of trait urgency and expectancies. *Psychology of Addictive Behaviors*, *18*(3), 269–274. http://doi.org/10.1037/0893-164X.18.3.269

Fischer, S., Peterson, C. M., & McCarthy, D. (2012). A Prospective Test of the Influence of Negative Urgency and Expectancies on Binge Eating and Purging. *Psychology of Addictive Behaviors*, *27*(1), 294–300. http://doi.org/10.1037/a0029323

Fischer, S., Settles, R., Collins, B., Gunn, R., & Smith, G. T. (2012). The role of negative urgency and expectancies in problem drinking and disordered eating: testing a model of comorbidity in pathological and at-risk samples. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *26*(1), 112–23. http://doi.org/10.1037/a0023460

Fischer, S., & Smith, G. T. (2008). Binge eating, problem drinking, and pathological gambling: Linking behavior to shared traits and social learning. *Personality and Individual Differences*, *44*(4), 789–800. http://doi.org/10.1016/j.paid.2007.10.008

Fischer, S., Smith, G. T., & Anderson, K. G. (2003). Clarifying the role of impulsivity in bulimia nervosa. *The International Journal of Eating Disorders*, *33*(4), 406–11. http://doi.org/10.1002/eat.10165

Frank, G. K. W., Reynolds, J. R., Shott, M. E., & O'Reilly, R. C. (2011). Altered temporal difference learning in bulimia nervosa. *Biological Psychiatry*, *70*(8), 728–735. http://doi.org/10.1016/j.biopsych.2011.05.011

Frank, S., Laharnar, N., Kullmann, S., Veit, R., Canova, C., Hegner, Y. L., … Preissl, H. (2010). Processing of food pictures: Influence of hunger, gender and calorie content. *Brain Research*, *1350*, 159–166. http://doi.org/10.1016/j.brainres.2010.04.030

Franken, I. H. a, & Muris, P. (2005). Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women. *Appetite*, *45*(2), 198–201. http://doi.org/10.1016/j.appet.2005.04.004

Fredrickson, B. L., & Branigan, C. (2005). Positive emotions broaden the scope of attention and thought- action repertoires Barbara. *Cognition & Emotion*, *19*(3), 313–332. http://doi.org/10.1080/02699930441000238

Friedman, D. P., Aggleton, J. P., & Saunders, R. C. (2002). Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: Combined anterograde and retrograde tracing study in the macaque brain. *Journal of Comparative Neurology*, *450*(4), 345–365. http://doi.org/10.1002/cne.10336

Frost, R. O., Goolkasian, G. A., Ely, R. J., & Blanchard, F. A. (1982). Depression, restraint and eating behavior. *Behaviour Research and Therapy*, *20*(2), 113–121. http://doi.org/10.1016/0005-7967(82)90111-5

Gabard-Durnam, L. J., Flannery, J., Goff, B., Gee, D. G., Humphreys, K. L., Telzer, E., … Tottenham, N. (2014). The development of human amygdala functional connectivity at rest from 4 to 23years: A cross-sectional study. *NeuroImage*, *95*, 193–207. http://doi.org/10.1016/j.neuroimage.2014.03.038

Galvan, A. (2010). Adolescent development of the reward system. *Frontiers in Human Neuroscience*, *4*(February), 6. http://doi.org/10.3389/neuro.09.006.2010

Galván, A. (2013). Current Directions in Psychological Science The Teenage Brain : Sensitivity to Rewards. http://doi.org/10.1177/0963721413480859

Galvan, A., Hare, T. a, Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*, *26*(25), 6885–6892. http://doi.org/10.1523/JNEUROSCI.1062-06.2006

García-García, I., Narberhaus, a, Marqués-Iturria, I., Garolera, M., Rădoi, a, Segura, B., … Jurado, M. a. (2013). Neural responses to visual food cues: insights from functional magnetic resonance imaging. *European Eating Disorders Review : The Journal of the Eating Disorders Association*, *21*(2), 89–98. http://doi.org/10.1002/erv.2216

Gardner, M., & Steinberg, L. (2005). Peer Influence on Risk Taking, Risk Preference, and Risky Decision Making in Adolescence and Adulthood: An Experimental Study. *Developmental Psychology*, *41*(4), 625–635. http://doi.org/10.1037/0012-1649.41.4.625

Ge, X., Lorenz, F. O., Conger, R. D., Elder, G. H., & Simons, R. L. (1994). Trajectories of stressful life events and depressive symptoms during adolescence. *Developmental Psychology*, *30*(4), 467–483. http://doi.org/10.1037/0012-1649.30.4.467

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., & Telzer, E. H. (2013). Early developmental emergence of human amygdala – prefrontal connectivity after maternal deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(39), 15638–15643. http://doi.org/10.1073/pnas.1307893110/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1307893110

Geier, C. F., Terwilliger, R., Teslovich, T., Velanova, K., & Luna, B. (2010). Immaturities in reward processing and its influence on inhibitory control in adolescence. *Cerebral Cortex*, *20*(7), 1613–1629. http://doi.org/10.1093/cercor/bhp225

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., … Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–863. http://doi.org/10.1038/13158

Glover, G. H., & Thomason, M. E. (2004). Improved Combination of Spiral-In/Out Images for BOLD fMRI. *Magnetic Resonance in Medicine*, *51*(4), 863–868. http://doi.org/10.1002/mrm.20016

Godart, N. T., Perdereau, F., Rein, Z., Berthoz, S., Wallier, J., Jeammet, P., & Flament, M. F. (2007). Comorbidity studies of eating disorders and mood disorders. Critical review of the literature. *Journal of Affective Disorders*, *97*(1–3), 37–49. http://doi.org/10.1016/j.jad.2006.06.023

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., … Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(21),

8174–9. http://doi.org/10.1073/pnas.0402680101

Goldstone, A. P., Prechtl de Hernandez, C. G., Beaver, J. D., Muhammed, K., Croese, C., Bell, G., … Bell, J. D. (2009). Fasting biases brain reward systems towards high-calorie foods. *The European Journal of Neuroscience*, *30*(8), 1625–35. http://doi.org/10.1111/j.1460-9568.2009.06949.x

Grant, B. F., & Dawson, D. A. (1997). Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the national longitudinal alcohol epidemiologic survey. *Journal of Substance Abuse*, *9*(1), 103–110. http://doi.org/10.1016/S0899-3289(97)90009-2

Greeno, C. G., & Wing, R. R. (1994). Stress-Induced Eating. *Psychological Bulletin*, *115*(3), 444–464.

Grilo, C. M., Pagano, M. E., Skodol, A. E., Sanislow, C. A., McGlashan, T. H., Gunderson, J. G., & Stout, R. L. (2007). Natural course of bulimia nervosa and of eating disorder not otherwise specified: 5-Year prospective study of remissions, relapses, and the effects of personality disorder psychopathology. *Journal of Clinical Psychiatry*, *68*(5), 738–746. http://doi.org/10.4088/JCP.v68n0511

Grose-fifer, J., Rodrigues, A., Hoover, S., Zottoli, T., Hodsoll, S., Viding, E., & Lavie, N. (2013). Attentional Capture by Emotional Faces. *Adv Cogn Psychol*, *9*(2), 81–91. http://doi.org/10.2478/v10053-008-0134-9.This

Guerrieri, R., Nederkoorn, C., Stankiewicz, K., Alberts, H., Geschwind, N., Martijn, C., & Jansen, A. (2007). The influence of trait and induced state impulsivity on food intake in normal-weight healthy women. *Appetite*, *49*(1), 66–73. http://doi.org/10.1016/j.appet.2006.11.008

Haase, L., Green, E., & Murphy, C. (2011). Males and females show differential brain activation to taste when hungry and sated in gustatory and reward areas. *Appetite*, *57*(2), 421–434. http://doi.org/10.1016/j.appet.2011.06.009

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(1), 4–26. http://doi.org/10.1038/npp.2009.129

Hadad, N. A., & Knackstedt, L. A. (2014). Addicted to palatable foods: Comparing the neurobiology of Bulimia Nervosa to that of drug addiction. *Psychopharmacology*, *231*(9), 1897–1912. http://doi.org/10.1007/s00213-014-3461-1

Haedt-Matt, A. A., & Keel, P. K. (2012). Revisiting the Affect Regulation Model of Binge Eating: A Meta-Analysis of Studies using Ecological Momentary Assessment. *Psychological Bulletin*, *137*(4), 660–681. http://doi.org/10.1037/a0023660

Hare, T. A., Tottenham, N., Davidson, M. C., Glover, G. H., & Casey, B. J. (2005). Contributions of amygdala and striatal activity in emotion regulation. *Biological Psychiatry*, *57*(6), 624–632. http://doi.org/10.1016/j.biopsych.2004.12.038

Hare, T. a., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J.

(2008). Biological Substrates of Emotional Reactivity and Regulation in Adolescence During an Emotional Go-Nogo Task. *Biological Psychiatry*, *63*(10), 927–934. http://doi.org/10.1016/j.biopsych.2008.03.015

Hare, T. a, Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science (New York, N.Y.)*, *324*(5927), 646–8. http://doi.org/10.1126/science.1168450

Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., & Weinberger, D. R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biological Psychiatry*, *53*(6), 494–501. http://doi.org/10.1016/S0006-3223(02)01786-9

Hariri, A. R., Tessitore, A., Mattay, V. S., Fera, F., & Weinberger, D. R. (2002). The amygdala response to emotional stimuli: a comparison of faces and scenes. *NeuroImage*, *17*(1), 317–323. http://doi.org/10.1006/nimg.2002.1179

Harrison, A., O'Brien, N., Lopez, C., & Treasure, J. (2010). Sensitivity to reward and punishment in eating disorders. *Psychiatry Research*, *177*(1–2), 1–11. http://doi.org/10.1016/j.psychres.2009.06.010

Hay, P. (2013). A systematic review of evidence for psychological treatments in eating disorders: 2005-2012. *The International Journal of Eating Disorders*, *46*(5), 462–9. http://doi.org/10.1002/eat.22103

Hay, P. J., & Claudino, A. M. (2010). Bulimia nervosa. *Clinical Evidence*, *2010*(January).

Hayaki, J. (2009). Negative reinforcement eating expectancies, emotion dysregulation, and symptoms of bulimia nervosa. *International Journal of Eating Disorders*, *42*(6), 552–556. http://doi.org/10.1002/eat.20646

Heatherton, T. F., & Baumeister, R. F. (1991). Binge eating as escape from self-awareness. *Psychological Bulletin*, *110*(1), 86–108. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1891520

Heatherton, T. F., Herman, C. P., & Polivy, J. (1991). Effects of physical threat and ego threat on eating behavior. *Journal of Personality and Social Psychology*, *60*(1), 138–43. http://doi.org/10.1037/0022-3514.60.1.138

Heatherton, T. F., Herman, C. P., & Polivy, J. (1992). Effects of distress on eating: the importance of ego-involvement. *Journal of Personality and Social Psychology*, *62*(5), 801–3. http://doi.org/10.1037/0022-3514.62.5.801

Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences*, *15*(3), 132–9. http://doi.org/10.1016/j.tics.2010.12.005

Hepworth, R., Mogg, K., Brignell, C., & Bradley, B. P. (2010). Negative mood increases selective attention to food cues and subjective appetite. *Appetite*, *54*(1), 134–42. http://doi.org/10.1016/j.appet.2009.09.019

Herman, C. P., & Mack, D. (1975). Restrained and unrestrained eating. *Journal of Personality*, *43*(4), 647–660. http://doi.org/10.1111/j.1467-6494.1975.tb00727.x

Higgins, E. T., Bond, R. N., Klein, R., & Strauman, T. (1986). Self-discrepancies and emotional vulnerability: how magnitude, accessibility, and type of discrepancy influence affect. *Journal of Personality and Social Psychology*, *51*(1), 5–15. http://doi.org/10.1037/0022-3514.51.1.5

Hohlstein, L. A., Smith, G. T., & Atlas, J. G. (1998). An application of expectancy theory to eating disorders: Development and validation of measures of eating and dieting expectancies. *Psychological Assessment*, *10*(1), 49–58. http://doi.org/10.1037/1040-3590.10.1.49

Hooper, C. J., Luciana, M., Conklin, H. M., & Yarger, R. S. (2004). Adolescents' performance on the Iowa Gambling Task: implications for the development of decision making and ventromedial prefrontal cortex. *Developmental Psychology*, *40*(6), 1148–1158. http://doi.org/10.1037/0012-1649.40.6.1148

Horn, N. R., Dolan, M., Elliott, R., Deakin, J. F. W., & Woodruff, P. W. R. (2003). Response inhibition and impulsivity: An fMRI study. *Neuropsychologia*, *41*(14), 1959–1966. http://doi.org/10.1016/S0028-3932(03)00077-0

Houben, K., & Jansen, A. (2011). Training inhibitory control. A recipe for resisting sweet temptations. *Appetite*, *56*(2), 345–9. http://doi.org/10.1016/j.appet.2010.12.017

Hudson, J. I., Hiripi, E., Pope, H. G., & Kessler, R. C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry*, *61*(3), 348–58. http://doi.org/10.1016/j.biopsych.2006.03.040

Huizinga, M., Dolan, C. V., & van der Molen, M. W. (2006). Age-related change in executive function: Developmental trends and a latent variable analysis. *Neuropsychologia*, *44*(11), 2017–2036. http://doi.org/10.1016/j.neuropsychologia.2006.01.010

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex - Developmental changes and effects of aging. *Brain Research*, *163*(2), 195–205. http://doi.org/10.1016/0006-8993(79)90349-4

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology*, *387*(2), 167–178. http://doi.org/10.1002/(SICI)1096-9861(19971020)387:2<167::AID-CNE1>3.0.CO;2-Z

Hwang, K., Velanova, K., & Luna, B. (2010). Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(46), 15535–15545. http://doi.org/10.1523/JNEUROSCI.2825-10.2010

Irwin, C. E. J., & Millstein, S. G. (1992). Risk-Taking Behaviors and Biopsychosocial Development During Adolescence. *Emotion, Cognition, Health, and Development in Children and Adolescents*, 75–102.

Jansen, A. (1998). A learning model of binge eating: cue reactivity and cue exposure. *Behaviour Research and Therapy*, *36*(3), 257–72. Retrieved from

http://www.ncbi.nlm.nih.gov/pubmed/9642846

Jansen, A., Nederkoorn, C., van Baak, L., Keirse, C., Guerrieri, R., & Havermans, R. (2009). High-restrained eaters only overeat when they are also impulsive. *Behaviour Research and Therapy*, *47*(2), 105–110. http://doi.org/10.1016/j.brat.2008.10.016

Johnson, C., & Larson, R. (1982). Bulimia: an analysis of moods and behavior. *Psychosomatic Medicine*, *44*, 341–351.

Jovicich, J., Czanner, S., Greve, D., Haley, E., Van Der Kouwe, A., Gollub, R., … Dale, A. (2006). Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. *NeuroImage*, *30*(2), 436–443. http://doi.org/10.1016/j.neuroimage.2005.09.046

Kane, T. a., Loxton, N. J., Staiger, P. K., & Dawe, S. (2004). Does the tendency to act impulsively underlie binge eating and alcohol use problems? An empirical investigation. *Personality and Individual Differences*, *36*(1), 83–94. http://doi.org/10.1016/S0191-8869(03)00070-9

Keel, P. K., Dorer, D. J., Franko, D. L., Jackson, S. C., & Herzog, D. B. (2005). Postremission predictors of relapse in women with eating disorders. *American Journal of Psychiatry*, *162*(12), 2263–2268. http://doi.org/10.1176/appi.ajp.162.12.2263

Keel, P. K., Mitchell, J. E., Miller, K. B., Davis, T. L., & Crow, S. J. (2000). Long-term outcome of bulimia nervosa. *Archives of General Psychiatry*, *56*, 63–69.

Kemps, E., & Wilsdon, A. (2010). Preliminary evidence for a role for impulsivity in cognitive disinhibition in bulimia nervosa. *Journal of Clinical and Experimental Neuropsychology*, *32*(5), 515–521. http://doi.org/10.1080/13803390903264122

Kessler, R. C., Avenevoli, S., & Ries Merikangas, K. (2001). Mood disorders in children and adolescents: an epidemiologic perspective. *Biological Psychiatry*, *49*(12), 1002–1014. http://doi.org/10.1016/S0006-3223(01)01129-5

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of. *Arch Gen Psychiatry*, *62*(June), 593–602. http://doi.org/10.1001/archpsyc.62.6.593

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders*, *29*(2–3), 85–96. http://doi.org/10.1016/0165-0327(93)90026-G

Kessler, R. C., McGonagle, K. a, Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., … Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*. http://doi.org/10.1001/archpsyc.1994.03950010008002

Kim, K. R., Ku, J., Lee, J.-H., Lee, H., & Jung, Y.-C. (2012). Functional and effective connectivity of anterior insula in anorexia nervosa and bulimia

nervosa. *Neuroscience Letters*, *521*(2), 152–7. http://doi.org/10.1016/j.neulet.2012.05.075

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, *12*(17), 3683–3687. http://doi.org/10.1097/00001756-200112040-00016

Kober, H., Mende-siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(33), 14811–14816. http://doi.org/10.1073/pnas.1007779107

Lavender, J. M., & Anderson, D. A. (2010). Contribution of emotion regulation difficulties to disordered eating and body dissatisfaction in college men. *International Journal of Eating Disorders*, *43*(4), 352–357. http://doi.org/10.1002/eat.20705

Laviola, G., Macrì, S., Morley-Fletcher, S., & Adriani, W. (2003). Risk-taking behavior in adolescent mice: Psychobiological determinants and early epigenetic influence. *Neuroscience and Biobehavioral Reviews*, *27*(1–2), 19–31. http://doi.org/10.1016/S0149-7634(03)00006-X

LeDoux, J. E. (1998). *The emotional brain: The mysterious underpinnings of emotional life*. *The emotional brain: The mysterious underpinnings of emotional life.* New York: Simon & Schuster. http://doi.org/10.2307/3953278

Lee, B. F. S., Heimer, H., Giedd, N., Lein, E. S., Šestan, N., Weinberger, D. R., & Casey, B. J. (2014). Adolescent mental health— Opportunity and obligation. *Science*, *346*(6209), 547–549. http://doi.org/10.1126/science.1260497

Lee, H., Heller, A. S., van Reekum, C. M., Nelson, B., & Davidson, R. J. (2012). Amygdala-prefrontal coupling underlies individual differences in emotion regulation. *NeuroImage*, *62*(3), 1575–1581. http://doi.org/10.1016/j.neuroimage.2012.05.044

Li, C. shan R., & Sinha, R. (2008). Inhibitory control and emotional stress regulation: Neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. *Neuroscience and Biobehavioral Reviews*, *32*(3), 581–597. http://doi.org/10.1016/j.neubiorev.2007.10.003

Liao, P.-C., Uher, R., Lawrence, N., Treasure, J., Schmidt, U., Campbell, I. C., … Tchanturia, K. (2009). An examination of decision making in bulimia nervosa. *Journal of Clinical and Experimental Neuropsychology*, *31*(4), 455–461. http://doi.org/10.1080/13803390802251378

Liston, C., Watts, R., Tottenham, N., Davidson, M. C., Niogi, S., Ulug, A. M., & Casey, B. J. (2006). Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cerebral Cortex*, *16*(4), 553–560. http://doi.org/10.1093/cercor/bhj003

Lock, J., Garrett, A., Beenhakker, J., & Reiss, A. L. (2011). Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. *The American Journal of Psychiatry*, *168*(1), 55–64.

http://doi.org/10.1176/appi.ajp.2010.10010056

Loeber, S., Grosshans, M., Herpertz, S., Kiefer, F., & Herpertz, S. C. (2013). Hunger modulates behavioral disinhibition and attention allocation to food-associated cues in normal-weight controls. *Appetite*, *71*, 32–39. http://doi.org/10.1016/j.appet.2013.07.008

Lopez, R. B., Hofmann, W., Wagner, D. D., Kelley, W. M., & Heatherton, T. F. (2014). Neural Predictors of Giving in to Temptation in Daily Life. *Psychological Science*, (April). http://doi.org/10.1177/0956797614531492

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Dev.*, *75*(5), 1357–1372. http://doi.org/10.1111/j.1467-8624.2004.00745.x

Macht, M. (1999). Characteristics of eating in anger, fear, sadness and joy. *Appetite*, *33*(1), 129–139. http://doi.org/10.1006/appe.1999.0236

Macht, M. (2008). How emotions affect eating: a five-way model. *Appetite*, *50*(1), 1–11. http://doi.org/10.1016/j.appet.2007.07.002

Macleod, C. M. (1991). Half a Century of Research on the Stroop Effect: An Integrative Review. *Psychological Bulletin*, *109*(2), 163–203. http://doi.org/Doi 10.1037//0033-2909.109.2.163

Macmillan, N. a, & Creelman, C. D. (2005). *Detection Theory: A User's Guide*. *Detection theory: A user's guide (2nd ed.).*

Marsh, R., Horga, G., Wang, Z., Wang, P., Klahr, K. W., Berner, L. A., … Peterson, B. S. (2011). An fMRI Study of Self-regulatary Control and Conflict resolution in Adolescents With Bulimia Nervosa. *American Journal of Psychiatry*, *168*(11), 1210–1220. http://doi.org/http://dx.doi.org/10.1176/appi.ajp.2011.11010094

Marsh, R., Zhu, H., Wang, Z., Skudlarski, P., & Peterson, B. S. (2007). A developmental fMRI study of self-regulatory control in Tourette's syndrome. *American Journal of Psychiatry*, *164*(6), 955–966. http://doi.org/10.1176/appi.ajp.164.6.955

Martin, C. a, Kelly, T. H., Rayens, M. K., Brogli, B. R., Brenzel, A., Smith, W. J., & Omar, H. a. (2002). Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*(12), 1495–502. http://doi.org/10.1097/00004583-200212000-00022

McRae, K., Gross, J. J., Weber, J., Robertson, E. R., Sokol-Hessner, P., Ray, R. D., … Ochsner, K. N. (2012). The development of emotion regulation: An fMRI study of cognitive reappraisal in children, adolescents and young adults. *Social Cognitive and Affective Neuroscience*, *7*(1), 11–22. http://doi.org/10.1093/scan/nsr093

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, a L. (2001). Error-Related Brain Activation during a Go / NoGo Response Inhibition Task. *Human Brain Mapping*, *12*(April 2000), 131–143. http://doi.org/10.1002/1097-0193(200103)12:3<131::AID-HBM1010>3.0.CO;2-C

Metropolitain Life Insurance Company. (1959). New weight standards for men and women. *Statistical Bulletin of the Metropolitan Life Insurance Company*, *40*, 1–4.

Meule, A., Lutz, A. P. C., Vögele, C., & Kübler, A. (2014). Impulsive reactions to food-cues predict subsequent food craving. *Eating Behaviors*, *15*(1), 99–105. http://doi.org/10.1016/j.eatbeh.2013.10.023

Mischel, W., Shoda, Y., & Rodriguez, M. I. (1989). Delay of gratification in children. *Science (New York, N.Y.)*, *244*(4907), 933–8. http://doi.org/10.1126/science.2658056

Mitchell, J. E., Agras, S., & Wonderlich, S. (2007). Treatment of bulimia nervosa: where are we and where are we going? *The International Journal of Eating Disorders*, *40*(2), 95–101. http://doi.org/10.1002/eat.20343

Mobbs, O., Van der Linden, M., D'Acremont, M., & Perroud, A. (2008). Cognitive deficits and biases for food and body in bulimia: investigation using an affective shifting task. *Eating Behaviors*, *9*(4), 455–61. http://doi.org/10.1016/j.eatbeh.2008.07.002

Mohr, H. M., Röder, C., Zimmermann, J., Hummel, D., Negele, A., & Grabhorn, R. (2011). Body image distortions in bulimia nervosa: Investigating body size overestimation and body size satisfaction by fMRI. *NeuroImage*, *56*(3), 1822–1831. http://doi.org/10.1016/j.neuroimage.2011.02.069

Monk, C. S., McClure, E. B., Nelson, E. E., Zarahn, E., Bilder, R. M., Leibenluft, E., … Pine, D. S. (2003). Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *NeuroImage*, *20*(1), 420–428. http://doi.org/10.1016/S1053-8119(03)00355-0

Nasser, J. A., Gluck, M. E., & Geliebter, A. (2004). Impulsivity and test meal intake in obese binge eating women. *Appetite*, *43*(3), 303–307. http://doi.org/10.1016/j.appet.2004.04.006

Nederkoorn, C., Smulders, F., Havermans, R., & Jansen, A. (2004). Exposure to binge food in bulimia nervosa: finger pulse amplitude as a potential measure of urge to eat and predictor of food intake. *Appetite*, *42*(2), 125–30. http://doi.org/10.1016/j.appet.2003.11.001

Nelson, E. E., & Guyer, A. E. (2011). The development of the ventral prefrontal cortex and social flexibility. *Developmental Cognitive Neuroscience*, *1*(3), 233–245. http://doi.org/10.1016/j.dcn.2011.01.002

Nelson, E. E., Leibenluft, E., McClure, E. B., & Pine, D. S. (n.d.). The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine*, *35*(2), 163–174. JOUR. http://doi.org/10.1017/S0033291704003915

O'Connor, D. B., Jones, F., Conner, M., McMillan, B., & Ferguson, E. (2008). Effects of daily hassles and eating style on eating behavior. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *27*(1 Suppl), S20–S31. http://doi.org/10.1037/0278-6133.27.1.S20

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural

responses during anticipation of a primary taste reward. *Neuron*, *33*, 815–826. http://doi.org/10.1016/S0896-6273(02)00603-7

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences*, *9*(5), 242–249. http://doi.org/10.1016/j.tics.2005.03.010

Oliver, G., Wardle, J., & Gibson, E. L. (2000). Stress and food choice: a laboratory study. *Psychosomatic Medicine*, *62*(6), 853–65. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11139006

Passamonti, L., Rowe, J. B., Schwarzbauer, C., Ewbank, M. P., von dem Hagen, E., & Calder, A. J. (2009). Personality predicts the brain's response to viewing appetizing foods: the neural basis of a risk factor for overeating. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(1), 43–51. http://doi.org/10.1523/JNEUROSCI.4966-08.2009

Passler, M., Isaac, W., & Hynd, G. (1985). Neuropsychological development of behavior attributed to frontal lobe functioning in children. *Developmental Neuropsychology*, *1*(4), 349–370. http://doi.org/10.1080/87565648509540320

Pearson, C. M., Wonderlich, S. a, & Smith, G. T. (2015). A risk and maintenance model for bulimia nervosa: From impulsive action to compulsive behavior. *Psychological Review*, *122*(3), 516–535. http://doi.org/10.1037/a0039268

Peciña, S., Schulkin, J., & Berridge, K. C. (2006). Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress? *BMC Biology*, *4*, 8. http://doi.org/10.1186/1741-7007-4-8

Perlman, S. B., & Pelphrey, K. A. (2011). Developing connections for affective regulation: Age-related changes in emotional brain connectivity. *Journal of Experimental Child Psychology*, *108*(3), 607–620. http://doi.org/10.1016/j.jecp.2010.08.006

Pessoa, L., Mckenna, M., Gutierrez, E., & Ungerleider, L. G. (2002). Neural processing of emotional faces requires attention.

Pettit, M. L., Jacob, S. C., Page, K. S., & Porras, C. V. (2010). An assessment of perceived emotional intelligence and eating attitudes among college students. *American Journal of Health Education*, *41*(1), 46–52. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-77949338763&partnerID=tZOtx3y1

Piazza, P. V., & Le Moal, M. (1998). The role of stress in drug self-administration. *Trends in Pharmacological Sciences*. http://doi.org/10.1016/S0165-6147(97)01115-2

Poe-Yamagata, E., & Butts, J. A. (1996). Female offenders in the juvenile justice system: Statistics summary, 25. http://doi.org/10.4135/9781452229300.n1312

Polivy, J., & Herman, C. P. (1993). Etiology of binge eating: Psychological mechanisms. In *Binge eating: Nature, assessment, and treatment* (pp. 173–205).

Prencipe, A., Kesek, A., Cohen, J., Lamm, C., Lewis, M. D., & Zelazo, P. D. (2011). Development of hot and cool executive function during the transition to adolescence. *Journal of Experimental Child Psychology*, *108*(3), 621–637. http://doi.org/10.1016/j.jecp.2010.09.008

Quinn, P. D., & Fromme, K. (2010). Self-regulation as a protective factor against risky drinking and sexual behavior. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *24*(3), 376–385. http://doi.org/10.1037/a0018547

Rakic, P., Bourgeois, J. P., & Goldman-Rakic, P. S. (1994). Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. *Progress in Brain Research*, *102*, 227–43. http://doi.org/10.1016/S0079-6123(08)60543-9

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(9), 2456–2477. http://doi.org/10.1093/brain/awr179

Resnick, M. D., Bearman, P. S., Blum, R. W., Bauman, K. E., Harris, K. M., Jones, J., … Udry, J. R. (1997). Protecting Adolescents From Harm. *JAMA: The Journal of the American Medical Association*, *278*(SEPTEMBER), 823–832. http://doi.org/10.1001/jama.1997.03550100049038

Reyna, V. F., & Rivers, S. E. (2008). Current Theories of Risk and Rational Decision Making Adolescent Risk Taking and the Science of Judgment and Decision Making. *Developmental Review*, *28*(1), 1–11. http://doi.org/10.1016/j.dr.2008.01.002

Ricca, V., Castellini, G., Fioravanti, G., Lo Sauro, C., Rotella, F., Ravaldi, C., … Faravelli, C. (2012). Emotional eating in anorexia nervosa and bulimia nervosa. *Comprehensive Psychiatry*, *53*(3), 245–251. http://doi.org/10.1016/j.comppsych.2011.04.062

Ridderinkhof, K. R., van der Molen, M. W., Band, G. P., & Bashore, T. R. (1997). Sources of interference from irrelevant information: a developmental study. *Journal of Experimental Child Psychology*, *65*(3), 315–341. http://doi.org/10.1006/jecp.1997.2367

Robbins, T. W., & Everitt, B. J. (1992). Functions of dopamine in the dorsal and ventral striatum. *Seminars in Neuroscience*, *4*(2), 119–127. http://doi.org/10.1016/1044-5765(92)90010-Y

Rogers, P. J., & Hill, A. J. (1989). Breakdown of dietary restraint following mere exposure to food stimuli: Interrelationships between restraint, hunger, salivation, and food intake. *Addictive Behaviors*, *14*, 387–397. http://doi.org/10.1016/0306-4603(89)90026-9

Rosval, L., Steiger, H., Bruce, K., Israël, M., Richardson, J., & Aubut, M. (2006). Impulsivity in women with eating disorders: problem of response inhibition, planning, or attention? *The International Journal of Eating Disorders*, *39*(7), 590–3. http://doi.org/10.1002/eat.20296

Rotella, F., Castellini, G., Montanelli, L., Rotella, C. M., Faravelli, C., & Ricca, V.

(2013). Comparison between normal-weight and overweight bulimic patients. *Eating and Weight Disorders : EWD*, *18*(4), 389–93. http://doi.org/10.1007/s40519-013-0053-8

Roy, M., Shohamy, D., & Wager, T. D. (2012). Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends in Cognitive Sciences*. http://doi.org/10.1016/j.tics.2012.01.005

Rubia, K., Lim, L., Ecker, C., Halari, R., Giampietro, V., Simmons, A., … Smith, A. (2013). Effects of age and gender on neural networks of motor response inhibition: From adolescence to mid-adulthood. *NeuroImage*, *83*, 690–703. http://doi.org/10.1016/j.neuroimage.2013.06.078

Rubia, K., Smith, A. B., Brammer, M. J., & Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *NeuroImage*, *20*(1), 351–358. http://doi.org/10.1016/S1053-8119(03)00275-1

Russchen, F. T., Bakst, I., Amaral, D. G., & Price, J. L. (1985). The amygdalostriatal projections in the monkey. An anterograde tracing study. *Brain Research*, *329*(1–2), 241–257. http://doi.org/10.1016/0006-8993(85)90530-X

Rydén, a, Sullivan, M., Torgerson, J. S., Karlsson, J., Lindroos, a-K., & Taft, C. (2003). Severe obesity and personality: a comparative controlled study of personality traits. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity*, *27*(12), 1534–40. http://doi.org/10.1038/sj.ijo.0802460

Sagaspe, P., Schwartz, S., & Vuilleumier, P. (2011). Fear and stop: A role for the amygdala in motor inhibition by emotional signals. *NeuroImage*, *55*(4), 1825–1835. http://doi.org/10.1016/j.neuroimage.2011.01.027

Schienle, A., Schäfer, A., Hermann, A., & Vaitl, D. (2009). Binge-eating disorder: reward sensitivity and brain activation to images of food. *Biological Psychiatry*, *65*(8), 654–61. http://doi.org/10.1016/j.biopsych.2008.09.028

Schneider, K. L., Panza, E., Appelhans, B. M., Whited, M. C., Oleski, J. L., & Pagoto, S. L. (2012). The emotional eating scale. Can a self-report measure predict observed emotional eating? *Appetite*, *58*, 563–566. http://doi.org/10.1016/j.appet.2012.01.012

Schotte, D. E., Cools, J., & McNally, R. J. (1990). Film-induced negative affect triggers overeating in restrained eaters. *Journal of Abnormal Psychology*, *99*, 317–320. http://doi.org/10.1037/0021-843X.99.3.317

Seeman, P., Bzowej, N. H., Guan, H. C., Bergeron, C., Becker, L. E., Reynolds, G. P., … Tourtellotte, W. W. (1987). Human brain dopamine receptors in children and aging adults. *Synapse (New York, N.Y.)*, *1*(January), 399–404. http://doi.org/10.1002/syn.890010503

Shapiro, J. R., Berkman, N. D., Brownley, K. A., Sedway, J. A., Lohr, K. N., & Bulik, C. M. (2007). Bulimia Nervosa Treatment: A systematic Review of Randomized Controlled Trials. *The International Journal of Eating Disorders*, *40*(2), 321–336. http://doi.org/10.1002/eat

Siep, N., Roefs, A., Roebroeck, A., Havermans, R., Bonte, M. L., & Jansen, A. (2009). Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behavioural Brain Research*, *198*(1), 149–58. http://doi.org/10.1016/j.bbr.2008.10.035

Silvers, J. A., Insel, C., Powers, A., Franz, P., Helion, C., Martin, R. E., … Ochsner, K. N. (2016). vlPFC–vmPFC–Amygdala Interactions Underlie Age-Related Differences in Cognitive Regulation of Emotion. *Cerebral Cortex*, bhw073. http://doi.org/10.1093/cercor/bhw073

Sim, L., & Zeman, J. (2004). Emotion Awareness and Identification Skills in Adolescent Girls With Bulimia Nervosa. *Journal of Clinical Child and Adolescent Psychology*, *33*(907840715), 760–771. http://doi.org/10.1207/s15374424jccp3304

Simpson, J. R., Ongür, D., Akbudak, E., Conturo, T. E., Ollinger, J. M., Snyder, a Z., … Raichle, M. E. (2000). The emotional modulation of cognitive processing: an fMRI study. *Journal of Cognitive Neuroscience*, *12 Suppl 2*, 157–70. http://doi.org/10.1162/089892900564019

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology*. http://doi.org/10.1007/s002130100917

Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. *Frontiers in Neuroendocrinology*, *26*(3–4), 163–174. http://doi.org/10.1016/j.yfrne.2005.10.003

Small, D. M., Jones-Gotman, M., & Dagher, A. (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *NeuroImage*, *19*(4), 1709–1715. http://doi.org/10.1016/S1053-8119(03)00253-2

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain : A Journal of Neurology*, *124*(Pt 9), 1720–1733. http://doi.org/10.1093/brain/124.9.1720

Smith, D. G., Xiao, L., & Bechara, A. (2012). Decision making in children and adolescents: impaired Iowa Gambling Task performance in early adolescence. *Developmental Psychology*, *48*(4), 1180–7. http://doi.org/10.1037/a0026342

Smith, G. T., Simmons, J. R., Flory, K., Annus, A. M., & Hill, K. K. (2007). Thinness and eating expectancies predict subsequent binge-eating and purging behavior among adolescent girls. *Journal of Abnormal Psychology*, *116*(1), 188–97. http://doi.org/10.1037/0021-843X.116.1.188

Smyth, J. M., Wonderlich, S. A., Heron, K. E., Sliwinski, M. J., Crosby, R. D., Mitchell, J. E., & Engel, S. G. (2007). Daily and momentary mood and stress are associated with binge eating and vomiting in bulimia nervosa patients in the natural environment. *Journal of Consulting and Clinical Psychology*, *75*, 629–638. http://doi.org/10.1037/0022-006X.75.4.629

Snyder, H. N. (2012). Arrest in the United States , 1990-2010. *US Department of*

Justice, (October), 1–26.

Somerville, L. H., Hare, T., & Casey, B. J. (2011). Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *Journal of Cognitive Neuroscience*, *23*(9), 2123–2134. http://doi.org/10.1162/jocn.2010.21572

Somerville, L. H., Jones, R. M., Ruberry, E. J., Dyke, J. P., Glover, G., & Casey, B. J. (2013). The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. *Psychol Sci*, *24*(8), 1554–1562. http://doi.org/10.1177/0956797613475633

Sowell, E. R. (2004). Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children. *Journal of Neuroscience*, *24*(38), 8223–8231. http://doi.org/10.1523/JNEUROSCI.1798-04.2004

Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L., & Toga, a W. (1999). In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience*, *2*(10), 859–861. http://doi.org/10.1038/13154

Spear, L. P. (2000). *The adolescent brain and age-related behavioral manifestations*. *Neuroscience and Biobehavioral Reviews* (Vol. 24). http://doi.org/10.1016/S0149-7634(00)00014-2

Spoor, S. T. P., Bekker, M. H. J., Van Strien, T., & van Heck, G. L. (2007). Relations between negative affect, coping, and emotional eating. *Appetite*, *48*(3), 368–76. http://doi.org/10.1016/j.appet.2006.10.005

Staiger, P., Dawe, S., & McCarthy, R. (2000). Responsivity to food cues in bulimic women and controls. *Appetite*, *35*(1), 27–33. http://doi.org/10.1006/appe.2000.0327

Stansfield, K. H., & Kirstein, C. L. (2006). Effects of novelty on behavior in the adolescent and adult rat. *Developmental Psychobiology*, *48*(1), 10–15. http://doi.org/10.1002/dev.20127

Steffensmeier, D. J., & Allan, E. A. (2016). Age and the Distribution of Crime Author (s): Darrell J . Steffensmeier , Emilie Andersen Allan , Miles D . Harer and Cathy Streifel Source : American Journal of Sociology , Vol . 94 , No . 4 (Jan ., 1989), pp . 803-831 Published by : The University o, *94*(4), 803–831.

Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental Review*, *28*(1), 78–106. http://doi.org/10.1016/j.dr.2007.08.002

Steinberg, L. (2010). A dual systems model of adolescent risk-taking. *Developmental Psychobiology*, *52*(3), 216–224. http://doi.org/10.1002/dev.20445

Stice, E., Killen, J. D., Hayward, C., & Taylor, C. B. (1998). Age of onset for binge eating and purging during late adolescence: a 4-year survival analysis. *Journal of Abnormal Psychology*, *107*(4), 671–675. http://doi.org/10.1037/0021-843X.107.4.671

Stoeckel, L. E., Weller, R. E., Cook, E. W., Twieg, D. B., Knowlton, R. C., & Cox, J. E. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *NeuroImage*, *41*(2), 636–647. http://doi.org/10.1016/j.neuroimage.2008.02.031

Strauman, T. J., Vookles, J., Berenstein, V., Chaiken, S., & Higgins, E. T. (1991). Self-discrepancies and vulnerability to body dissatisfaction and disordered eating. *Journal of Personality and Social Psychology*, *61*(6), 946–956. http://doi.org/10.1037/0022-3514.61.6.946

Striegel-Moore, R. H., Silberstein, L. R., & Rodin, J. (1986). Toward an understanding of risk factors for bulimia. *American Psychologist*, *41*(3), 246–263. http://doi.org/10.1037/0003-066X.41.3.246

Stuber, G. D., Sparta, D. R., Stamatakis, A. M., van Leeuwen, W. A., Hardjoprajitno, J. E., Cho, S., … Bonci, A. (2011). Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. *Nature*, *475*, 377–380. http://doi.org/10.1038/nature10194

Svaldi, J., Griepenstroh, J., Tuschen-Caffier, B., & Ehring, T. (2012). Emotion regulation deficits in eating disorders: A marker of eating pathology or general psychopathology? *Psychiatry Research*, *197*(1–2), 103–111. http://doi.org/10.1016/j.psychres.2011.11.009

Swartz, J. R., Carrasco, M., Wiggins, J. L., Thomason, M. E., & Monk, C. S. (2014). Age-related changes in the structure and function of prefrontal cortex-amygdala circuitry in children and adolescents: A multi-modal imaging approach. *NeuroImage*, *86*, 212–220. http://doi.org/10.1016/j.neuroimage.2013.08.018

Tangney, J. P., Baumeister, R. F., & Boone, A. L. (2004). High self-control predicts good adjustment, less pathology, better grades, and interpersonal success. *Journal of Personality*, *72*(2), 271–324. http://doi.org/10.1111/j.0022-3506.2004.00263.x

Tarazi, F. I., & Baldessarini, R. J. (2000). Comparative postnatal development of dopamine D1, D2, and D4 receptors in rat forebrain. *International Journal of Developmental Neuroscience*, *18*(1), 29–37. http://doi.org/10.1016/S0736-5748(99)00108-2

Team, R. D. C. (2013). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.* Retrieved from http://www.r-project.org.org

Teicher, M. H., Krenzel, E., Thompson, A. P., & Andersen, S. L. (2003). Dopamine receptor pruning during the peripubertal period is not attenuated by NMDA receptor antagonism in rat. *Neuroscience Letters*, *339*(2), 169–171. http://doi.org/10.1016/S0304-3940(02)01475-1

Teslovich, T., Freidl, E. K., Kostro, K., Weigel, J., Davidow, J. Y., Riddle, M. C., … Mayer, L. (2014). Probing behavioral responses to food: Development of a food-specific go/no-go task. *Psychiatry Research*, *219*(1), 166–170. http://doi.org/10.1016/j.psychres.2014.04.053

Teslovich, T., Mulder, M., Franklin, N. T., Ruberry, E. J., Millner, A., Somerville, L. H., … Casey, B. J. (2014). Adolescents let sufficient evidence accumulate before making a decision when large incentives are at stake. *Developmental Science*, *17*(1), 59–70. http://doi.org/10.1111/desc.12092

Tottenham, N., Hare, T. a., & Casey, B. J. (2011). Behavioral assessment of emotion discrimination, emotion regulation, and cognitive control in childhood, adolescence, and adulthood. *Frontiers in Psychology*, *2*(MAR), 1–9. http://doi.org/10.3389/fpsyg.2011.00039

Tymula, A., Rosenberg Belmaker, L. A., Roy, A. K., Ruderman, L., Manson, K., Glimcher, P. W., & Levy, I. (2012). Adolescents' risk-taking behavior is driven by tolerance to ambiguity. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(42), 17135–40. http://doi.org/10.1073/pnas.1207144109

Van den Eynde, F., Koskina, A., Syrad, H., Guillaume, S., Broadbent, H., Campbell, I. C., & Schmidt, U. (2012). State and trait food craving in people with bulimic eating disorders. *Eating Behaviors*, *13*(4), 414–417. http://doi.org/10.1016/j.eatbeh.2012.07.007

Van Leijenhorst, L., Moor, B. G., Op de Macks, Z. A., Rombouts, S. A. R. B., Westenberg, P. M., & Crone, E. A. (2010). Adolescent risky decision-making: Neurocognitive development of reward and control regions. *NeuroImage*, *51*(1), 345–355. http://doi.org/10.1016/j.neuroimage.2010.02.038

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A. R. B., & Crone, E. A. (2010). What motivates the adolescent? brain regions mediating reward sensitivity across adolescence. *Cerebral Cortex*, *20*(1), 61–69. http://doi.org/10.1093/cercor/bhp078

Vannucci, a, Nelson, E. E., Bongiorno, D. M., Pine, D. S., Yanovski, J. a, & Tanofsky-Kraff, M. (2015). Behavioral and neurodevelopmental precursors to binge-type eating disorders: support for the role of negative valence systems. *Psychological Medicine*, *45*(14), 2921–36. http://doi.org/10.1017/S003329171500104X

Velten, E. (1968). A laboratory task for induction of mood states. *Behaviour Research and Therapy*, *6*(4), 473–482. http://doi.org/10.1016/0005-7967(68)90028-4

Vohs, K. D., & Heatherton, T. F. (2000). Self-Regulatory Failure :, (21), 249–254.

Volkow, N. D., Fowler, J. S., Wang, G. J., Telang, F., Logan, J., Jayne, M., … Swanson, J. M. (2010). Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *NeuroImage*, *49*(3), 2536–2543. http://doi.org/10.1016/j.neuroimage.2009.10.088

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Wong, C., … Pappas, N. R. (1999). Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *The Journal of Pharmacology and Experimental Therapeutics*, *291*(1), 409–415. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&d

opt=Citation&list_uids=10490931

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-Subcortical Pathways Mediating Successful Emotion Regulation. *Neuron*, *59*(6), 1037–1050. http://doi.org/10.1016/j.neuron.2008.09.006

Wagner, A., Aizenstein, H., Venkatraman, V. K., Bischoff-Grethe, A., Fudge, J., Christopher May, J., … Kaye, W. H. (2010). Altered striatal response to reward in bulimia nervosa after recovery. *International Journal of Eating Disorders*, *43*(4), 289–294. http://doi.org/10.1002/eat.20699

Wagner, D. D., Boswell, R. G., Kelley, W. M., & Heatherton, T. F. (2012). Inducing negative affect increases the reward value of appetizing foods in dieters. *Journal of Cognitive Neuroscience*, *24*(7), 1625–33. http://doi.org/10.1162/jocn_a_00238

Waller, G., & Osman, S. (1998). Emotional eating and eating psychopathology among non-eating-disordered women. *International Journal of Eating Disorders*, *23*(4), 419–424. http://doi.org/10.1002/(SICI)1098-108X(199805)23:4<419::AID-EAT9>3.0.CO;2-L

Wallis, D. J., & Hetherington, M. M. (2004). Stress and eating: the effects of ego-threat and cognitive demand on food intake in restrained and emotional eaters. *Appetite*, *43*(1), 39–46. http://doi.org/10.1016/j.appet.2004.02.001

Wardle, J., Steptoe, A., Oliver, G., & Lipsey, Z. (2000). Stress, dietary restraint and food intake. *Journal of Psychosomatic Research*, *48*(2), 195–202. http://doi.org/10.1016/S0022-3999(00)00076-3

Wartenburger, I., Heekeren, H. R., Preusse, F., Kramer, J., & Meer, E. Van Der. (2009). NeuroImage Cerebral correlates of analogical processing and their modulation by training. *NeuroImage*, *48*(1), 291–302. http://doi.org/10.1016/j.neuroimage.2009.06.025

Weickert, C. S., Webster, M. J., Gondipalli, P., Rothmond, D., Fatula, R. J., Herman, M. M., … Akil, M. (2007). Postnatal alterations in dopaminergic markers in the human prefrontal cortex. *Neuroscience*, *144*(3), 1109–1119. http://doi.org/10.1016/j.neuroscience.2006.10.009

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *18*(1), 411–418. http://doi.org/9412517

Whiteside, U., Chen, E., Neighbors, C., Hunter, D., Lo, T., & Larimer, M. (2007). Difficulties regulating emotions: Do binge eaters have fewer strategies to modulate and tolerate negative affect? *Eating Behaviors*, *8*(2), 162–169. http://doi.org/10.1016/j.eatbeh.2006.04.001

Wierenga, C. E., Ely, A., Bischoff-Grethe, A., Bailer, U. F., Simmons, A. N., & Kaye, W. H. (2014). Are Extremes of Consumption in Eating Disorders Related to an Altered Balance between Reward and Inhibition? *Frontiers in Behavioral Neuroscience*, *8*, 1–11. http://doi.org/10.3389/fnbeh.2014.00410

Williams, P. G., Holmbeck, G. N., & Greenley, R. N. (2002). Adolescent health psychology. *Journal of Consulting and Clinical Psychology*, *70*(3), 828–842. http://doi.org/10.1037//0022-006X.70.3.828

Wonderlich, S. A., Engel, S. G., Peterson, C. B., Robinson, M. D., Crosby, R. D., Mitchell, J. E., … Simonich, H. K. (2008). Examining the conceptual model of integrative cognitive-affective therapy for BN: Two assessment studies. *International Journal of Eating Disorders*, *41*(8), 748–754. http://doi.org/10.1002/eat.20551

Wonderlich, S. A., Peterson, C. B., Crosby, R. D., Smith, T. L., Klein, M. H., Mitchell, J. E., & Crow, S. J. (2014). A randomized controlled comparison of integrative cognitive-affective therapy (ICAT) and enhanced cognitive-behavioral therapy (CBT-E) for bulimia nervosa. *Psychological Medicine*, *44*(3), 543–53. http://doi.org/10.1017/S0033291713001098

Wozniak, J. R., & Lim, K. O. (2006). Advances in white matter imaging: A review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neuroscience and Biobehavioral Reviews*, *30*(6), 762–774. http://doi.org/10.1016/j.neubiorev.2006.06.003

Wu, M., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H.-C. (2013). Inhibitory control in bulimic-type eating disorders: a systematic review and meta-analysis. *PloS One*, *8*(12), e83412. http://doi.org/10.1371/journal.pone.0083412

Yeomans, M. R., & Coughlan, E. (2009). Mood-induced eating. Interactive effects of restraint and tendency to overeat. *Appetite*, *52*, 290–298. http://doi.org/10.1016/j.appet.2008.10.006

Yokum, S., Ng, J., & Stice, E. (2011). Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. *Obesity (Silver Spring, Md.)*, *19*(9), 1775–83. http://doi.org/10.1038/oby.2011.168

Zellner, D. A., Saito, S., & Gonzalez, J. (2007). The effect of stress on men's food selection. *Appetite*, *49*(3), 696–699. http://doi.org/10.1016/j.appet.2007.06.013

Zellner, D. a, Loaiza, S., Gonzalez, Z., Pita, J., Morales, J., Pecora, D., & Wolf, A. (2006). Food selection changes under stress. *Physiology & Behavior*, *87*(4), 789–93. http://doi.org/10.1016/j.physbeh.2006.01.014